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ACUTE POISONING IN NORTHERN VIETNAM: EPIDEMIOLOGIC, DIAGNOSTIC AND THERAPEUTIC ASPECTS

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ABSTRACT

Poisoning is a major health problem in northern Vietnam. The aims of these studies were to improve prevention, differential diagnosis and treatment of this threat to the public.

A hospital-based retrospective study of poisoning emergencies admitted to the first Poison Control Center (PCC) in Vietnam during the years 1999 and 2003 (Paper I) revealed that a vast majority of the poisoning emergencies occurred at home. Pesticides, hypnotic pharmaceuticals and heroin were among the most commonly involved toxic agents and entailed an increased risk of a fatal outcome. The frequently recorded severe toxic symptoms, including coma, respiratory failure, hypotension and seizures, indicate a need for more specialized clinical poisoning units with intensive care facilities in Vietnam.

A cross-sectional community-based study from a rural part of Vietnam (Paper IV) pointed out that the availability and accessibility of pesticides constitute the main risk factor for poisoning among ordinary people in Vietnam. A second important source of toxins in the rural area of Vietnam is its poisonous flora and fauna. Other common risk factors for poisoning were the availability and inadequate storage of hazardous household products and self-medication of pharmaceuticals purchased at retail pharmacies without professional consultation.

A retrospective study of 60 consecutive patients envenomed by *Bungarus multicinctus* treated at the intensive care unit (ICU) of the PCC during the 4-year period 2000-2003 (Paper II) demonstrated that bites by this particular krait species commonly occur in rural areas and during night-time. The first symptoms developed within a wide time-range of 0.5 to 24 hours. The dilatation of the pupils was often maximal and extremely persistent in some cases. A majority of the patients developed generalized muscle paralysis and 87% of the study population needed mechanical ventilation. The new and surprising finding of a high rate of significant hyponatremia makes frequent laboratory monitoring and sometimes prompt sodium replacement imperative, and the severe clinical features recorded indicate an urgent need for a specific antivenom.

A controlled clinical trial of a novel antivenom against *B. multicinctus* during a three-year period (2004-2006) at the ICU of the PCC (Paper III) clearly demonstrated its favourable efficacy and acceptable safety. The prospective study also confirmed the new finding in paper II of a high risk for development of significant hyponatremia after snakebite by this particular species.

In conclusion, the epidemiological hospital- and community-based studies provided fundamental information needed for improved poisoning prevention in Vietnam. The retrospective study identified important clinical information regarding envenoming by *B. multicinctus*. The new finding of a high rate of clinically significant hyponatremia makes repeated monitoring of electrolytes and in some cases prompt sodium replacement imperative. The controlled clinical trial demonstrated the efficacy and safety of the novel specific antivenom against *B. multicinctus* and thereby set up a principal treatment routine for patients envenomed by *B. multicinctus*.

Keywords: acute poisoning, epidemiology, risk factor, antivenom, snakebite, *Bungarus multicinctus*, Vietnam

LIST OF PUBLICATIONS

I. Hung HT, Du NT, Höjer J. The first Poison Control Center in Vietnam: experiences of its initial years. Southeast Asian J Trop Med Public Health 2008; 39: 310-318.

II. Hung HT, Höjer J, Du NT. Clinical features of 60 consecutive ICU-treated patients envenomed by *Bungarus multicinctus*. Southeast Asia J Trop Med Public Health 2009; 40: 518-524.

III. Hung HT, Höjer J, Kiem TX, Du NT. A controlled clinical trial of a novel antivenom in patients envenomed by *Bungarus multicinctus.* J Med Toxicol. Published online 01 April 2010.

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CONTENTS

LIST OF ABBREVIATIONS

AChE	Acetylcholine receptors
ICU	Intensive Care Unit
IPCS	International Programme on Chemical Safety
OP	Organophosphorus
PCC	Poison Control Center
PLA2	Phospholipases A_2
WHO	World Health Organization

1 INTRODUCTION

1.1 EPIDEMIOLOGY OF ACUTE POISONING IN DEVELOPING COUNTRIES

Poisoning is a significant threat to public health globally and constitutes a common cause of medical emergencies. Defined as drug overdose, food poisoning, or symptomatic exposure to an environmental toxin, poisoning is an extensive health care problem. According to WHO data, an estimated 350,000 people died worldwide in 2002 from unintentional poisoning. In the year 2000, poisoning was the ninth most common cause of death in young adults worldwide and there were more than three million cases of poisoning, with a mortality rate of approximately 8% [1]. It has been estimated that over 90% of such fatalities occur in developing countries [1].

The panorama of frequently occurring toxins and exposure hazards differs considerably from country to country. Thus, epidemiological studies with toxicological surveillance data for each country are necessary to determine the countries' specific problems and risks, so that preventive measures can be taken. However, toxico-epidemiological data from developing countries are sparse [1].

Most epidemiological studies of poisoning in developing countries have been based on either hospital treated cases or on data from poison information centers. These studies have shown that pesticides are the most important toxins world-wide due to wide spread use and high mortality rates. Poisoning by pharmaceuticals, household products and natural toxins are also common and important causes of morbidity and mortality in developing countries [2, 3].

Vietnam is a developing country with approximately 86 million inhabitants. Its population is relatively young, 39% consisting of children and adolescents, while 17% are elderly [4]. In general Vietnam is an agricultural country and farmers account for nearly 75% of its population, forming a large market for biocides and other toxic chemicals. As a result of ready availability of poisons and the lack of an effective control strategy, poisoning has become a major health problem throughout the country. However, reliable data on poisoning patterns in Vietnam are sparse and incomplete, and to our knowledge no study on clinical toxicological issues from this country has been previously published in any international medical journal. Moreover, potentially hazardous factors for poisonings have not been thoroughly studied.

Pesticides

Agrochemical pesticides are a major public health problem throughout the developing world [5]. Many farming households have stocks of pesticides readily available for impulsive acts. Storage facilities and knowledge of the toxicity of the agents are frequently poor [6, 7].

Insecticides

Organophosphorus (OP) pesticides were responsible for a majority of the deaths in most series of self-poisoning cases in the developing countries, particularly those from rural areas [8-10].

Carbamates are less toxic than OP pesticides. However, a series of seven deaths due to furathiocarb self-poisoning was reported from Korea in the year 1999 [11].

Poisoning with the organochlorines endosulfan and endrin has recently become an important cause of seizures in parts of South Asia [12, 13]. They cause a status epilepticus that is usually unresponsive to standard treatment, requiring general anaesthesia. These pesticides are rapidly metabolized by the body and therefore, if the patient can be supported through the status epilepticus, prognosis is good with few residual complications [14].

As for other pesticides, the compounds abamectin and ivermectin (both avermectins) are used for the control of parasite infections in crops and cattle. Out of 19 patients reported to a Taiwanese poison control centre between 1993 - 1997, seven showed marked toxicity with coma, respiratory failure and hypotension. One patient died. Fourteen cases (six severe) were categorized as self-poisoning [15].

Pyrethrins are less toxic than most other insecticides. A few cases of self-poisoning have been reported from India [16].

Herbicides

The dipyridyl pesticides paraquat and diquat are highly toxic. Paraquat has been reported to be a problem in many parts of the world, including Korea [17, 18], Malaysia [19], Singapore [20], Sri Lanka [21], Taiwan [22] and Thailand [23].

Glyphosate is another type of herbicide. Two case series from Taiwan have described 181 patients with such poisoning. The most common symptoms reported was

gastrointestinal tract irritation. Severe cases showed cardiogenic shock, respiratory insufficiency, renal failure, and metabolic acidosis. Eighteen patients died [24, 25].

Rodenticides

Aluminium phosphide is toxic after ingestion because contact with water in the stomach liberates phosphine gas. It has become one of the commonest means of self-poisoning in northern India [26]. A study from Chandigarh, India, showed that it is also a common means of self-harm amongst adolescents, with a mortality rate of 59% [27].

Long-acting 'superwarfarin' compounds such as brodifacoum cause long-term coagulopathies and have been used for self-poisoning world-wide. This type of rodenticide poisoning has, for example, been reported from Hong Kong [28].

Pharmaceutical agents

Medication overdose and poisoning have most commonly been reported from cities in the developing world [2, 3, 29]. Outside the cities, these poisonings are relatively uncommon. In general, overdoses of pharmaceuticals have a relatively good prognosis, particularly when compared to pesticides. While barbiturates were an extremely common means of self-poisoning worldwide during the 1970s [30, 31], benzodiazepines, antiepileptics, antidepressants and other psychoactive drugs are much more frequently reported today.

Of the analgesic drugs, paracetamol (acetaminophen) is a common poison in some regions of the developing world. Papers on paracetamol poisoning have been reported from Hong Kong [32], Malaysia [33] and Taiwan [34].

Herbal or traditional medicines

Traditional Chinese medications of various forms have been reported to be commonly used for self-poisoning in Hong Kong and Taiwan [35, 36].

Household products

There have been few studies looking at domestic chemicals, but in some African and Asian communities they have been reported to constitute a major health problem [37, 38]. Household products include for example kerosene oil used for lighting, agents for cleaning and bleaching, and strong acids and alkalis used for drain clearing.

Kerosene is a common household energy source throughout the developing world, often kept in unsafe non-child-proof containers. These products are a major problem because of accidental poisoning among young children [39] and to a lesser extent, due to self-poisoning by adults. Pulmonary complications and deaths may result from their aspiration.

Of other substances, potassium permanganate is a common household disinfectant that has been used for self-harm in Hong Kong with fatal hepatorenal complications [40].

Corrosives

Corrosive chemicals are widely used in the industry and the homes. They cause intense damage to the pharynx, oesophagus and stomach, often producing perforations. Patients may die from peritonitis or mediastinitis, or from pulmonary complications such as fistula formation and pneumonia.

This type of poisoning is quite different from other forms of acute poisoning. Patients poisoned by pesticides and pharmaceutical agents typically present with an acute crisis and if the course is not fatal, they will have few complications. In contrast, survivors of acute corrosive poisoning often require extensive surgical follow-up for their GI complications [41, 42].

A Taiwanese group has reported their results after treating 75 patients for caustic oesophageal strictures or post-caustic resections over 15 years [43]. Most patients had taken HCl and all adults (62 patients) had taken the corrosive intentionally. Eitghty-seven percent of the operations were done as elective procedures. There were no deaths and the outcome after these complicated procedures was described as 'good' in 90% of the cases.

A large series of patients poisoned by domestic chemicals has been reported from Malaysia of whom the majority had ingested NaOH [44]. Again complicated bowel surgery procedures were required after the acute resuscitation. Ten patients died acutely, 11 required replacement surgery.

Natural toxins

Plants

Poisonous plants have been used for centuries for homicide, suicide and inducing abortion [45]. Ingestion of some plants have become locally popular methods for self-

harm, but none so serious and life threatening as the remarkable epidemic of yellow oleander seed poisoning currently occurring in Sri Lanka [46].

Poisonous animals

Snake-bites are well-known medical emergencies in many parts of the world, especially in rural areas. Agricultural workers and children are the most affected. The snake-bite mortality rate is particularly high in South-East Asia [47]. It is clear that in many parts of the South East Asian region, snakebite is an important medical emergency and cause of hospital admission. It results in the death or chronic disability of many active young people, especially those involved in farming and plantation work. However, the exact magnitude or the true rate of mortality and acute and chronic morbidity from snake-bite remains uncertain, because of inadequate reporting from almost every part of the region. Moreover, despite its importance, there have been few proper clinical studies of snake-bite compared to almost all other tropical diseases.

Hymenopterans, as for example wasps, constitute a biologically extremely fascinating animal group due to their omnipresence in practically every living space and to the fact that they comprise the medically most significant venomous animals in the world. In the US and also in Europe, hymenopteran stings are the cause of the majority of deaths due to venomous animals [48].

1.2 *BUNGARUS MULTICINCTUS* ENVENOMATION

1.2.1 Medically important venomous snakes in Vietnam

Snakebite is a largely unrecognized public health problem that causes significant challenges for medical management, especially in the tropical region [49]. In Vietnam, two snake families have poisonous members, the Elapidae and the Viperidae. The family Elapidae includes the king cobra (*Ophiophagus hannah*), the familiar cobras (Chinese/Taiwan cobra-*Naja atra*, monocellate cobra-*N. kaouthia*, and Thai or Isan spitting cobra-*N. siamensis*), and the kraits (*Bugarus multicinctus, B. candidus,* and *B fasciatus)*. Among these venomous species, *Ophiophagus Hannah*, *Naja atra* and especially *Bugarus multicinctus* are responsible for many bites and much morbidity and mortalitty in northern Vietnam. Besides cobras and kraits, there are some sea venomous

snakes found along the coast of Vietnam, especially 3 species, namely: *Hydrophis cyanocinctus, Lapemis hardwickii* and *Enhydrina schistose*. The vipers (family viperidae) include some species: *Calloselasma rhodostoma, Trimeresurus albolabris, T. popeiorum,* and *T. wagleri*.

1.2.2 *Bugarus multicinctus* and its geographical distribution

The elapid snakes include, among others, the kraits represented by 12 species worldwide within the single genus *Bungarus*. The kraits are generally unagressive nocturnal animals that frequently enter rural houses. *B. multicinctus* (Chinese or many-banded krait) are found in many Asian countries, including southern China, Taiwan, Hong Kong, and the northern parts of Laos, Myanmar, and Vietnam [49]. Its habitats include low plains and hilly regions up to an altitude of 1,300 meters. Along the back of this snake is a series of black to bluish-black saddle-shaped markings separated by 30-50 narrow white bands sprinkled with dark spot. The belly is pure white. The maximum length is 1.84 meters [49] (Fig. 1).

Figure 1. *Bungarus multicinctus*.

1.2.3 Venoms of *B. multicinctus*

Snake venoms contain a large variety of enzymes (proteases, phospholipases, etc), non-enzymatic polypeptide toxins (post-synaptic neurotoxins, cardiotoxins etc), amino acids, biogenic amines, carbohydrates, lipids, nucleosides, nucleotides and

metals. Most of these components have no obvious role in the pathogenesis of envenoming in human patients.

The most important and best known effects of *B. multicinctus* venoms are neurotoxic activities. Neurotoxicity has been defined as "a structural change or a functional adverse response of the nervous system to a chemical, biological or physical agent" [50]. In *B. multicinctus* venoms, the following classes of neurotoxins have been identified:

α - bungarotoxin (*Postsynaptically active toxin - toxin binding selectively to nicotinic acetylcholine receptors)*

The α-bungarotoxin, a "three finger" protein, has been extremely well-characterized. This postsynaptically active toxin binds (essentially irreversibly) selectively to peripheral nicotinic acetylcholine receptors (AChR) at the postsynaptic membrane of the neuromuscular junction and prevent the binding of acetylcholine. The effect is to produce a non-depolarising type of neuromuscular blockade. This toxin, conveniently known as α-neurotoxin, has been an invaluable tool in the study of the nicotinic acetylcholine receptor [51].
Envenoming bites by snakes whose venoms are rich in α-neurotoxins cause a neuromuscular weakness with very rapid onset and of potentially fatal depth. Reversal of paralysis, even in severely envenomed victims, occurs approximately 24 hours after the bite, provided respiration is maintained, and recovery can be accelerated by the administration of antivenom or anticholinesterase [51]. The postsynaptic toxins that bind to nicotinic AChR cause no structural damage to any part of the nervous system or its target cell and any long-term sequelae to the bite must be considered due to the presence of other toxic fractions in the crude venom or a consequence of other types of complications.

β - bungarotoxin (*Presynaptically active toxin - toxic phospholipases A_2)*

Phospholipases A_2 (PLA2) are common components of snake venoms. Snake venom phospholipases A_2 fall into two major classes. Class I phospholipases A_2 may be isolated from the venoms of elapid snakes and their close relatives the sea snakes. Class II phospholipases A_2 may be isolated from venoms of viperid and crotalid snakes. Class I phospholipases A_2 are homologous with pancreatic phospholipases

A_2. Class II phospholipases A_2 are homologous with the phospholipases A_2 of platelets, neutrophils, and other cell types.
The venom glands of snakes are derived from salivary glands, and so it is not unreasonable to suppose that the primary purpose of venom phospholipases is digestive. Snakes cannot chew their prey. Prey items are swallowed whole and so the ability to inoculate into a prey item a highly active phospholipase provides a means whereby the digestive process can begin very early. But, although the venom phospholipases A_2 may originally have been purely digestive in function, many possess a wide range of other activities. They may, for example, be anticoagulant, cytotoxic, haemolytic, neurotoxic or myotoxic. This thesis is primarily concerned the neurotoxic and myotoxic activities of the toxic phospholipases A_2.
The neurotoxic phospholipases A_2 are commonly referred to as β-neurotoxins to distinguish them from the α-neurotoxins, which bind to junctional nicotinic AChR at the vertebrate neuromuscular junction. The β-neurotoxins are presynaptically active, inducing neuromuscular weakness by attacking the motor-nerve terminal.

Chang and Lee (1963) were the first to isolate and pharmacologically characterize the β-bungarotoxin from the venom of the Taiwan banded krait, *Bungarus multicinctus*. However, it was not until 1978 that the structure and amino acid sequence of β-bungarotoxin was analysed in detail. It is a basic protein, with a molecular weight of 21,800 kD consisting of two dissimilar polypeptide subunits [52]. A phospholipase A_2 subunit named the A-chain and a non-phospholipase A_2 subunit named the B-chain that is homologous to bovine pancreatic trypsin inhibitor.

Failure of neuromuscular transmission caused by neurotoxic phospholipases

Studies on β-bungarotoxin have shown beyond doubt that the target for the neurotoxic phospholipases A_2 is the nerve terminal rather than the axon of the motor neuron. The definitive evidence for this is that, at the cessation of spontaneous respiration following poisoning by β-bungarotoxin, electrical discharges can still be recorded from the phrenic nerve [52]. This simple observation demonstrates that fatal poisoning involves neither damage to the lower motor neuron nor the impairment of axonal conduction of the action potential. There is also extensive evidence that the presynaptically active neurotoxic phospholipases A_2 do not block AChR on the postsynaptic surface of the neuromuscular junction [53].

1.2.4 Clinical manifestations of *B. multicinctus* envenoming

The clinical characteristics arising from bites by *Bungarus multicinctus* (many-banded krait, Chinese krait) have rarely been described [54, 55]. This species is an important cause of snakebite mortality in Southern China. In Guangxi Zhuang autonomous region (close to the northern border of Vietnam), 8.4% of snakebites were caused by *B. multicinctus* and, 36.3% of these developed paralytic symptoms. The mortality rate was 10% [56]. In Taiwan, 8% of bites were caused by this species between 1904 and 1971 with a 23% case fatality rate [49]. Bites occur mainly at night time, but only 16% were inflicted in the home [56]. Local symptoms are negligible. The bite is felt as a prick followed by slight itching, numbness or redness but with minimal swelling. Nausea and vomiting may develop about 30 minutes later and neurotoxic symptoms within 1-4 hours after the bite. These include ptosis, inability to speak and swallow, "trimus" (inability to open the mouth), chest tightness, breathlessness, generalized aching and weakness of the limbs. Other symptoms include headache, dizziness, thirst, confusion, throat pain, laryngeal spasm and drowsiness. In fatal cases not treated with antivenom, the interval between bite and death ranges from 6-23 hours [49].

In northern Vietnam *B. multicinctus* is the only krait species of medical significance in humans [57]. Knowledge of the clinical features of envenomation by this snake is important for early diagnosis of severe conditions and for effective treatment of the snakebite. The symptoms are commonly observed as follows:

Local symptoms and signs at the bitten part of the body:

Envenomation by this krait produces no or only minimal local symptoms, except fang marks (Fig. 2).

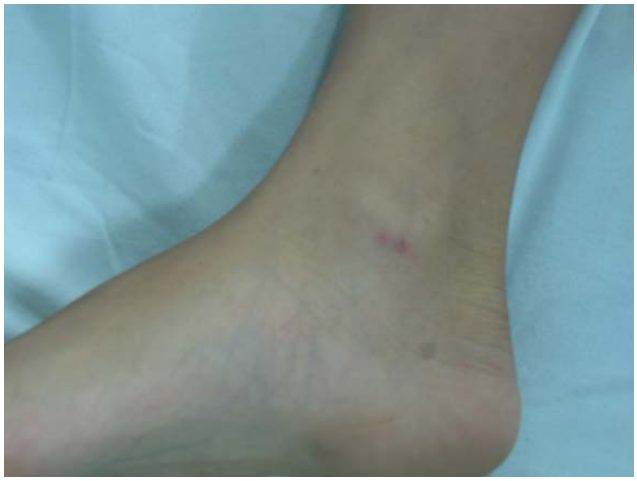

Figure 2. Fang mark after a bite by *Bungarus multicinctus*.

Systemic symptoms and signs:

Neurological manifestations include paraesthesia, throat pain, ptosis (Fig. 3), external ophthalmoplegia, mydriasis (Fig. 4), paralysis of facial muscles and other muscles innervated by the cranial nerves, nasal voice or aphonia, regurgitation through the nose, difficulty in swallowing secretions, generalized aching, respiratory and generalized flaccid paralysis (Fig. 5), and parasympathetic abnormalities. Non-neurotoxic complications include conjunctivitis, and ventilator associated pneumonia.

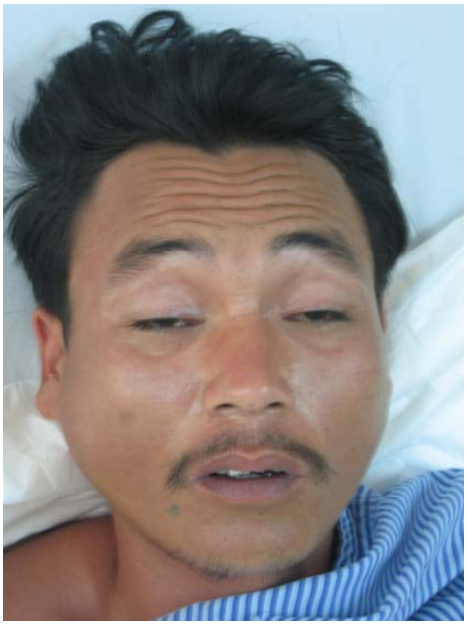

Figure 3. Ptosis after a bite by *Bungarus multicinctus*.

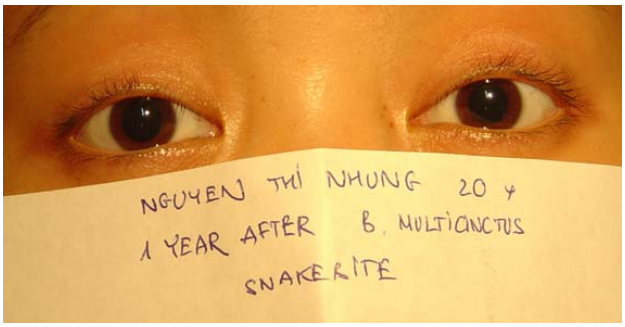

Figure 4. Persistent mydriasis one year after envenomation by *Bungarus multicinctus*.

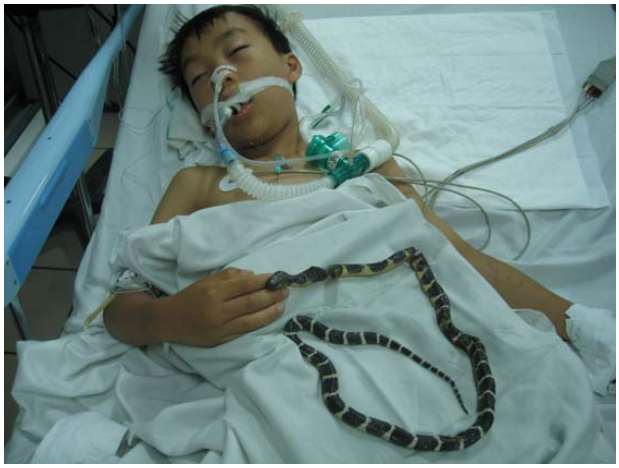

Figure 5. Respiratory and generalised flaccid paralysis after a bite by the later killed krait placed on the patient.

1.3 ANTIVENOM THERAPY FOR ENVENOMATION BY *BUNGARUS MULTICINCTUS*

Supportive care is an important part of the management of snakebites, but antivenom administration is the mainstay therapy in the majority of medically significant cases of envenomation. Such specific therapy may dramatically reduce the consequences of the envenomation [58-60]. Although antivenoms against *B. multicinctus* are available in China and Taiwan, clinical reports regarding their efficacy have only rarely been published [54, 56, 61]. In some series of cases antivenom treatment has been tried after snakebites by other *Bungarus* species, but with rather conflicting clinical results [62, 63]. In Vietnam, no specific antivenom against *B. multicinctus* has been available until recently, when it was developed and produced for clinical use. The indication for antivenom administration in patients envenomed by *B. multicinctus* is the development of neurotoxic signs (Table 1).

Table 1. Indications for antivenom treatment after snakebite [47]

Antivenom treatment is recommended if and when a patient with proven or suspected snake-bite develops one or more of the following signs:

Systemic envenoming

- *Haemostatic abnormalities:* Spontaneous systemic bleeding (clinical), coagulopathy (20WBCT or other laboratory tests such as prothrombin time) or thrombocytopenia (<100 x 109/litre or 100 000/cu mm) (laboratory).
- ***Neurotoxic signs:*** **ptosis, external ophthalmoplegia, paralysis etc (clinical).**
- *Cardiovascular abnormalities:* hypotension, shock, cardiac arrhythmia (clinical), abnormal ECG.
- *Acute kidney injury (renal failure):* oliguria/anuria (clinical), rising blood creatinine/ urea (laboratory).
- *(Haemoglobin-/myoglobin-uria:)* dark brown urine (clinical), urine dipsticks, other evidence of intravascular haemolysis or generalised rhabdomyolysis (muscle aches and pains, hyperkalaemia) (clinical, laboratory).
- Supporting laboratory evidence of systemic envenoming (see above).

Local envenoming

- Local swelling involving more than half of the bitten limb (in the absence of a tourniquet) within 48 hours of the bite. Swelling after bites on the digits (toes and especially fingers).
- Rapid extension of swelling (for example, beyond the wrist or ankle within a few hours of bite on the hands or feet).
- Development of an enlarged tender lymph node draining the bitten limb

Antivenom adverse reactions

A proportion of patients, usually more than 10%, develop a reaction either early (within a few hours) or late (five days or more) after being given antivenom. The risk of reactions is dose-related, except in rare cases in which there has been sensitization (IgE-mediated Type I hypersensitivity) by previous exposure to animal serum, for example, to equine antivenom, tetanus-immune globulin or rabies-immune globulin.

(1) ***Early anaphylactic reactions***: Usually within 10-180 minutes of starting antivenom administration, the patient begins to itch (often over the scalp) and develops urticaria, dry cough, fever, nausea, vomiting, abdominal colic, diarrhoea and tachycardia. A minority of these patients may develop severe life-threatening anaphylaxis: hypotension, bronchospasm and angio-oedema. Fatal reactions have probably been under-reported as death after snake-bite is usually attributed to the venom and patients may not be monitored carefully after treatment. In most cases, these reactions are not truly "allergic". They are not IgE-mediated type I hypersensitivity reactions to horse proteins as there is no evidence of specific IgE, either by skin testing or radioallergosorbent tests (RAST). Complement activation by IgG aggregates or residual Fc fragments or direct stimulation of mast cells or basophils by antivenom protein are more likely mechanisms for these reactions.

(2) ***Pyrogenic (endotoxin) reactions:*** These reactions usaully develop 1-2 hours after treatment. The symptoms include shaking chills (rigors), fever, vasodilatation and hypotension. Febrile convulsions may be precipitated in children. These reactions are caused by pyrogenic contamination during the manufacturing process. They are commonly reported.

(3) ***Late (serum sickness type) reactions:*** These adverse reactions develop 1-12 (mean 7) days after treatment. Clinical features include fever, nausea, vomiting, diarrhoea, itching, recurrent urticaria, arthralgia, myalgia, lymphadenopathy, periarticular swellings, mononeuritis multiplex, proteinuria with immune complex nephritis and, rarely, encephalopathy. Patients who suffer early adverse reactions and are promptly treated with antihistamines and corticosteroid are less likely to develop late reactions.

Treatment of antivenom adverse reactions [47]

Early anaphylactic and pyrogenic antivenom reactions: Epinephrine (adrenaline) is given intramuscularly (into upper lateral thigh) in an initial dose of 0.5 mg for adults and 0.01 mg/kg body weight for children. As severe, life-threatening anaphylaxis may evolve rapidly, epinephrine (adrenaline) should be given at the very first sign of a reaction, even when only a few spots of urticaria have appeared or at the start of itching, tachycardia or restlessness. The dose can be repeated every 5-10 minutes if the patient's condition is deteriorating.

Additional treatment: After epinephrine (adrenaline), an antihistamine, such as chlorphenamine, should be given IV followed by intravenous hydrocortisone. The corticosteroid is unlikely to act for several hours, but may prevent recurrent anaphylaxis.

In pyrogenic reactions the patient must also be cooled physically and with antipyretics. Intravenous fluids should be given to correct a relative hypovolaemia.

Treatment of late (serum sickness) reactions: Late adverse reactions may respond to a 5-day course of oral antihistamine. Patients who fail to respond in 24-48 hours should be given a 5-day course of a corticosteroid.

2 AIMS

Poisoning is a major health problem in northern Vietnam. The principal aims of these studies were to improve prevention, differential diagnosis and treatment of this threat to the public.

2.1 SPECIFIC AIMS FOR PAPER I

To investigate the poisoning pattern in northern Vietnam by studying the frequency and characteristics of poisoning emergencies admitted to the only Poison Control Center (PCC) in Vietnam during its first five years (1999 – 2003).

2.2 SPECIFIC AIMS FOR PAPER II

To assess the frequency and clinical features of patients admitted to the PCC in Hanoi during 2000 – 2003 after envenomation by *Bungarus multicinctus*.

2.3 SPECIFIC AIMS FOR PAPER III

To assess the efficacy of a newly produced antivenom against *Bungarus multicinctus* and to investigate its possible side effects.

2.4 SPECIFIC AIMS FOR PAPER IV

To identify the most commonly occurring toxin exposure hazards and other risks of acute poisoning in the rural area of northern Vietnam.

3 METHODS

3.1 METHODS FOR PAPER I

In this retrospective study, the medical records of all patients admitted to the PCC in Hanoi during the years 1999 and 2003 because of poisoning were carefully reviewed.

Poisoning was defined as drug overdose, food poisoning, or exposure to any environmental toxic substance. A study protocol was developed from the existing IPCS-Case/Incident/Request Format (http://www.who.int/ipcs/poisons/Minform-Eng.XLS)[64]. The protocol was subsequently refined and covered all pertinent data including demographics, type of poisoning, clinical findings, treatment, and outcome.

The patients either presented directly to the PCC or were referred from other hospitals in northern Vietnam. The severity of each case of poisoning was defined upon admission, using the 5-graded Poisoning Severity Score (PSS) criteria of the IPCS [65].

The outcome in each patient was classified into one of three categories: 1. recovery, 2. sequela (an impairment of functioning corresponding to a performance category of 2-4 on the 5-graded Glasgow-Pittsburgh Outcome Scale [66, 67] on discharge from hospital), or 3. death during hospitalization.

3.2 METHODS FOR PAPER II

In this retrospective study the medical records of all patients treated at the intensive care unit (ICU) of the PCC for envenoming by *B. multicinctus* during the 4-year period 2000-2003 were carefully reviewed. In a majority of the cases, the type of snake was determined either at the hospital by investigation of a snake specimen brought to the PCC or by the patient in connection with the bite. In some cases the snake was never seen, however, and the diagnosis was then established by the circumstances of the bite together with the presence of typical clinical features. A predetermined study protocol was developed. Pertinent data of each case were recorded, including demographics, the time and circumstances of the bite, the body parts bitten, symptoms and signs, laboratory findings, any complications, length of time spent in the ICU, and the outcome. The severity of each case was defined using the 5-graded (0-4) Poisoning

Severity Score (PSS) [65]. Treatment measures documented in the medical records, such as mechanical ventilation, were also noted.

3.3 METHODS FOR PAPER III

This prospective controlled clinical trial was carried out during a three-year period (2004-2006) at the ICU of the PCC at Bach Mai Hospital in Hanoi. For ethical reasons and because the antivenom was not clinically available until 2006, the study was not randomized or blinded. All patients who fulfilled the inclusion criteria during the first two years of the study were prospectively enrolled, carefully monitored and treated with optimal supportive therapy in the ICU (control group). The patients who entered the study during the third year were treated with antivenom therapy in addition to supportive care (antivenom group). The patients were enrolled on the basis of the following criteria: 1. envenomation by *B. multicinctus*, 2. presence of clinical signs of systemic envenomation (neuromuscular signs), and 3. (during the year 2006) provision of written informed consent (by close relative if the patient was unable to do so). Clinical data including a number of defined clinical and laboratory examinations, were recorded for each case in a predetermined standardized protocol during the entire 3-year study period. The severity of the symptoms on recruitment was defined on the basis of the 5-graded (0-4) Poisoning Severity Score (PSS) [65].

During the year 2006, the patients were informed about the possible benefits and risks of the antivenom treatment and were able to withdraw at any time during the trial for any reason. Five to ten ampoules of antivenom, depending on the severity of muscle paralysis, were diluted with isotonic glucose solution to a total of 50 ml and then infused intravenously by electric pump during a period of one hour. The patients were monitored continuously during and after the infusion to assess the efficacy of the treatment and any adverse reactions. Six to 8 hours after the end of the infusion, a second infusion was administered, under similar conditions, if no clinical improvement or adverse reaction had been noted. Clinical examinations, in accordance with the study protocol, were performed at least twice daily up to discharge. The patients were also followed up one month later and readmitted if associated symptoms developed or became worse.

Predefined outcome endpoints were number of patients requiring mechanical ventilation, duration of mechanical ventilation, length of stay in the ICU, duration of a defined degree of muscle paralysis, and number of patients who developed a ventilator-associated pneumonia. The study was conducted in accordance with the WHO Good Clinical Practice guidelines and the Declaration of Helsinki. The study design and the form for the written consent were approved by the Ethics Committee of Hanoi Medical University.

Antivenom

Venom pools from more than 100 specimens of *B. candidus* and *B. multicinctus* of different sizes, ages and sexes were collected from Vietnam. After milking, venoms were immediately lyophilized and then detoxified with glutaraldehyde, filtered, and stored at 4°C in bottles. Immunization of horses with increasing doses of the antigen described above was performed once a month for 7 months. The immunoglobulin fraction from each of the pooled horse plasma samples was pepsin-digested and then salt-precipitated to produce $F(ab')_2$ fragments. The antivenom was supplied in liquid form, 2000 units per ampoule. The antivenom was approved for the use under discussion in the manuscript by the National Institute for Control of Medico Biological Products, Ministry of Health in Vietnam, but it has not yet become a commercial product.

3.4 METHODS FOR PAPER IV

This cross-sectional population-based epidemiological study was conducted in the Phu Tho province in northern Vietnam during the year 2008. This province is situated at the apex of the Red river delta linking Hanoi with the Northern mountainous provinces (Fig. 6). Its area is 3,519 km^2, corresponding to 1% of the whole country, and its population in the year 2006 was about 1.3 million or approximately 1.5% of all Vietnamese. The rural population of Phu Tho accounts for 85% of its total inhabitants, a proportion which resembles that of entire Vietnam. There are 13 local administrative regions (11 districts, one city, and one township) in the Phu Tho province, comprising a total of 273 communes. Among these, two out of twelve communes in the Lam Thao district were chosen as the study setting. The inhabitants of these two communes are representative of Vietnam regarding occupational distribution and the communes are

typical of Vietnam regarding density of population and nature of agriculture. The main crops in the study area are rice and different kinds of vegetables, just as in the main parts of rural Vietnam.

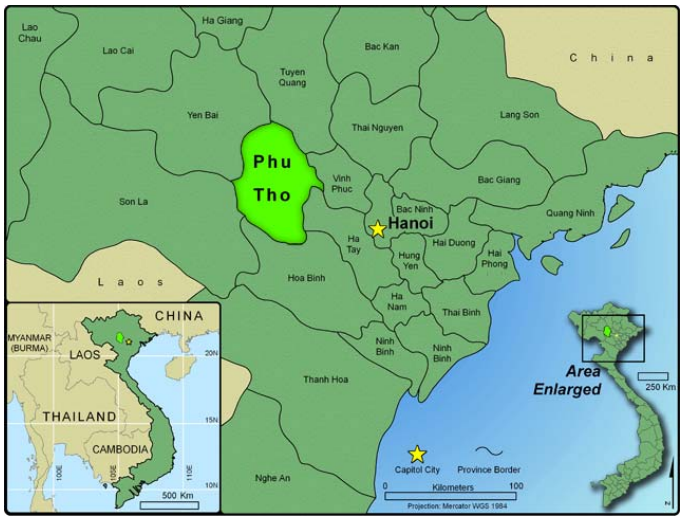

Fig 6. Map of Vietnam and Phu Tho province

The study population initially comprised 1,000 randomly selected households in the two above mentioned communes, which consisted of 23 villages. After giving their informed consent, 942 households comprising 3,814 individuals, were finally enrolled in the study. The data collection methods included face-to-face interviews, using a structured questionnaire, and reality observations following a structured checklist. The questionnaire covered information on demographic features and on general epidemiological points, poisoning events, and risk factors for poisoning. Poisoning was defined as drug overdose, food poisoning, or any symptomatic exposure to an environmental toxic substance. The checklist included presence of any pesticides, other toxic chemicals, pharmaceuticals, or drugs of abuse at home, and also safety keeping methods, equipment for preparation and use of pesticides, and existence of poisonous plants or animals.

4 RESULTS

4.1 EPIDEMIOLOGY OF POISONING IN NORTHERN VIETNAM

4.1.1 Frequency, characteristics and management of poisoning emergencies admitted to the PCC in Hanoi during its first 5 years (paper I)

The annual number of admitted poisoned patients increased during the initial period of the first PCC in Vietnam, from 313 in 1999 (59.5% of the total number of admissions) to 1,523 in 2003 (91.3% of all admissions). The female : male ratio during the five-year period was approximately 1:1. The largest number of poisoned patients was found in the age-group 15-24 years.

In the year 1999, unemployed persons and agricultural workers were the most common occupational groups among the poisoned patients. Four years later, students and people working in service occupations increased dramatically (Table 2). A finding that did not change during the 5-year period was that a vast majority of the toxic exposures occurred at home (74.1%).

Table 2. Occupational distributions of the poisoned patients during the years 1999 and 2003.

Occupation	1999, n=313	2003, n=1523	Total, n=1836	
	n	n	n	%
Service occupations	57	474	531	28.9
Student	54	358	412	22.4
None	85	256	341	18.6
Agricultural worker	82	250	332	18.1
Industrial worker	24	160	184	10.0
Other or unknown	11	20	36	2.0

Concerning the types of toxic agents causing the poisoning, the most common in 1999 were pharmaceuticals and pesticides. In 2003 food poisoning predominated, followed by pharmaceuticals, toxins from poisonous animals (mostly snake venom), and pesticides (Table 3).

The clearly predominating route of exposure was ingestion. Bites and stings from poisonous animals were also relatively common. Injection of heroin and inhalation of toxic gases were examples of less common routes of exposure (Table 4).

Table 3. Types of toxic agents involved in the cases of poisoning.

Type of toxin	**1999, n=313**	**2003, n=1523**	**Total, n=1836**	
	n	**n**	**n**	**%**
Food/beverage	19	626	645	35.1
Pharmaceuticals	160	460	620	33.8
Poisonous animals (mostly snakes)	29	202	231	12.6
Pesticides (including rodenticides)	61	107	168	9.1
Drug of abuse (heroin)	13	72	85	4.6
Household/leisure products	6	12	18	1.0
Industrial / commercial products	8	7	15	0.8
Environmental contamination	1	9	10	0.5
Plants	3	6	9	0.5
Other or unknown	13	22	35	1.9

Table 4. Routes of exposure among the poisoned patients during the years 1999 and 2003.

Route of exposure	1999, n=313	2003, n=1523	Total, n=1836	
	n	n	n	%
Ingestion	269	1190	1459	78.6
Bite	28	133	161	8.8
Sting	0	64	64	3.5
Injection	8	53	61	3.3
Inhalation	5	29	34	1.8
Cutaneous	0	7	7	0.4
Other or unknown	3	47	50	2.7

Compared with accidental toxic exposures, the number of deliberate poisonings was larger in 1999 but smaller during 2003. In total, these two types of the toxic exposure were approximately equally common. Suicidal poisoning constituted approximately one third of all cases of poisoning (Table 5).

Table 5. Intentional versus unintentional poisoning.

Circumstance of exposure	1999, n=313	2003, n=1523	Total, n=1836	
	n	n	n	%
Unintentional (accidental)	82	823	905	49.3
Intentional-suicide	178	393	571	31.1
Intentional-misuse, abuse, malicious	34	234	268	14.6
Unknown	19	73	92	5.0

A majority of the poisoned patients displayed mild symptoms (PSS grade 1) on admission to the PCC. However, more than a quarter of the total number of poisoned patients showed pronounced clinical signs of poisoning and some even had life-threatening symptoms. During the year 1999, the relative proportion of patients with severe poisoning (PSS grades 3-4) was higher than during 2003 (16.9% and 8.9%, respectively, $p<0.001$) (Table 6).

Table 6. Poisoning Severity Score (PSS) on admission to the PCC.

Severity of poisoning (PSS)	**1999, n=313**	**2003, n=1523**	**Total, n=1836**	
	n	**n**	**n**	**%**
None (0)	58	77	135	7.4
Minor (1)	163	1051	1214	66.1
Moderate (2)	39	259	298	16.2
Severe (3)	53	135	188	10.2
Fatal (4)	0	1	1	0.1

The occurrence of specified poisoning-induced symptoms recorded during the hospital stay is shown in Table 7. The most common signs of serious poisoning were a reduced level of consciousness, respiratory failure, hypotension, rhabdomyolysis, and seizures.

Table 7. The distribution of specified poisoning-induced symptoms recorded at the PCC.

Poisoning-induced symptoms	1999, n=313	2003, n=1523	Total, n=1836	
	n	n	n	%
Reduced level of consciousness*	83	235	318	17.3
Respiratory failure	64	83	147	8.0
Hypotension (systolic BP <90 mmHg)	33	96	129	7.0
Rhabdomyolysis	12	111	123	6.7
Seizures	15	73	88	4.8
Bradycardia (heart rate <50)	5	28	33	1.8
Ventricular arrhythmia†	13	19	32	1.7
Acute renal failure	10	18	28	1.5
Acute hepatic failure	3	16	19	1.0
Gastrointestinal hemorrhage	2	15	17	0.9

*Glasgow Coma Scale score <13

†Including 26 patients with frequent ventricular extrasystoles and 6 with ventricular tachycardia.

The poisoning specific-treatments most commonly used during the study years were decontamination measures such as administration of cathartics, activated charcoal, gastric lavage and skin decontamination. Intensive care measures such as mechanical ventilation and dialysis were used less frequently. Specific antidotes were given in approximately 5% of all cases (Table 8).

Table 8. Use of therapeutic interventions in the poisoned patients at the PCC.

Treatment	1999, n=313	2003, n=1523	Total, n=1836	
	n	n	n	%
Induced emesis	12	71	83	4.5
Gastric lavage	191	364	555	30.2
Charcoal, single dosage	143	437	580	31.6
Charcoal, repeated dosage	46	25	71	3.8
Cathartic	195	433	628	34.2
Skin decontamination	23	66	89	4.8
Irrigation of eye	4	12	16	0.9
Endotracheal intubation	64	83	147	8.0
Mechanical ventilation	56	64	120	6.5
Antidote administration	16	80	96	5.2
Hemodialysis	8	23	31	1.7

The mean stay in the PCC was 2.10 ± 0.99 days. Of the total of 1,836 poisoned patients, 1,322 (72.1%) were discharged within 24 hours. However, 140 patients (7.6%) required hospitalization for more than one week. The longest treatment duration was 62 days.

The main outcome among the poisoned patients treated at the PCC during 1999 and 2003 is shown in Table 9. The hospital mortality rate was higher in 1999 (1.9%) than during 2003 (1%), but the difference was not statistically significant. The fatalities mainly resulted from poisoning by hypnotic pharmaceuticals (phenobarbital in 5 cases), heroin overdose and some very toxic pesticides.

Table 9. Main outcome among the cases of poisoning at the PCC.

Main outcome	1999, n=313	2003, n=1523	Total, n=1836	
	n	n	n	%
Recovery	306	1499	1805	98.3
Sequela	1	9	10	0.5
Fatal	6	15	21	1.1

4.1.2 Potentially hazardous environmental factors for poisoning in rural Vietnam (paper IV)

Among the total study population of 3,814 persons, 1,921 or 50.4% were male. Their mean age was 32.7 ± 19.7 (range 1 - 94) years. The study population consisted of 942 families (households). The mean number of family members was 4.0 $\pm$ 1.2 (range 1-8) people. A majority of the study population were agricultural workers. Other common occupations were students, industrial laborers, and commercial workers (Table 10).

Table 10. The occupational distribution of the study population.

Occupation	n (%)
Agricultural worker	1,981 (51.9)
Student	917 (24.0)
Industrial worker	332 (8.7)
None	254 (6.7)
Commercial worker	97 (2.5)
Small children	48 (1.3)
Housewife/husband	7 (0.2)
Other or unknown	178 (4.7)
Total	3,814 (100)

Hazardous exposures to toxic agents commonly occurred. Pesticides and other chemicals used in agriculture were the most frequently involved toxic compounds (Table 11).

Table 11. Occurrence of hazardous exposures to toxic agents.

Toxic agent	Household, n (%)
Insecticides	783 (83.1)
Herbicides	601 (63.8)
Household products	223 (23.7)
Rodenticides	202 (21.4)
Adulterant chemicals	23 (2.4)
Industrial chemicals	22 (2.3)
Preservation chemicals	19 (2.0)
Toxic gases	1 (0.1)

Of the total study population, 438 individuals (11.5%) recalled having suffered from at least one symptomatic episode of acute poisoning. The toxic agents reported to be most commonly involved in these incidents were different kinds of pesticides (Table 12).

Table 12. Toxic agents reported to have been involved in the most recently occurring symptomatic poisoning episode among the study population.

Toxic agent	n (%)
Pesticides	301 (68.7)
Pollution	8 (1.8)
Other chemicals used in agriculture	5 (1.1)
Food poisoning	4 (0.9)
Industrial chemicals	2 (0.5)
Medications	1 (0.2)
Other or unrecognized	117 (26.7)

Among the studied households, 48 (5.1%) reported to have at least one family member with some chronic medical consequence of a poisoning. None of these sequelae was life-threatening, but rather graded was as mild to moderate. Examples of these chronic symptoms were general tiredness, and weakness and numbness of distal extremities. They were most commonly (71%) consequences of exposures to pesticides.

Concerning the presence of toxic agents in the homes, different pesticides were again the most common. Other common toxic agents kept at home were chemical household products and other agrochemicals (Table 13).

Table 13. Toxic agents kept at home.

Toxic agent	Presence in household, n (%)
Insecticides	294 (31.2)
Chemical household products	274 (29.1)
Herbicides	44 (4.7)
Rodenticides	21 (2.2)
Adulterant chemicals	6 (0.6)
Industrial chemicals	4 (0.4)
Preservation chemicals	3 (0.3)
Other toxic chemicals	119 (12.6)

A majority of the households had obtained knowledge of safety keeping processes directly from sellers. Only in barely one third of the households had the family members received the necessary knowledge from responsible persons such as agricultural expand personnel. Approximately 7% of the households had not been given any information concerning safety keeping methods at all (Table 14).

Table 14. Sources of information concerning methods of safety keeping of toxic agents at home.

Source of information	Households, n (%)
Sellers	479 (50.8)
Agriculture expand personnel	303 (30.2)
Self-learning from other sources	293 (31.1)
Media	275 (29.2)
Relatives, friends, neighbors	97 (10.3)
None	66 (7.0)

Among the studied households, 204 (21.7%) reported that they had kept poisonous chemicals in places accessible to children, and 505 (53.6%) had never locked chemical storage boxes or drawers. One hundred and thirty-one households (13.9%) had not kept hazardous chemicals in their original containers, and among these 33 (3.5%) had used food containers to keep poisonous chemicals. More than a fourth of the households (27.7%) did not have the habit of explaining to their children about the risks with toxic chemicals.

The risk of overdosage of pharmaceuticals was also recorded in the study. Nearly half of the households always kept medications at home, but only approximately one fourth had any medical safe-box. A large proportion of the households (56.2%) reported that prescriptions were not necessary for purchasing pharmaceuticals.

Some common habits of the studied households put their members in danger of poisoning by natural toxins. Among these, frequent use of herbs, and raising and eating poisonous animals, were the most important hazardous practices (Table 15).

Table 15. Possible risk factors for natural toxin poisoning.

Possible risk	Households, n (%)
Collection and ingestion of unusual herbs*	292 (30.1)
Use of poisonous animals as food	241 (25.6)
Honey collection from bee and wasp nests	125 (13.3)
Raising poisonous animals	86 (9.1)
Ingestion of animal gallbladders	30 (3.2)

*After advice from quacks in approximately half of the households.

When observing the reality with their own eyes, the interviewers found that pesticides were present in 369 of the households (39%). Pesticides were most commonly kept in containers without any lock (97.5%). The presence of pharmaceuticals at home was observed in 564 households (60%). Besides bees' nests, which were common, venomous snakes were seen to be raised in 75 of the households and poisonous toads in 14.

4.2 IMPORTANT POISONING – ENVENOMING BY *B. MULTICINCTUS*

4.2.1 Clinical features of 60 patients envenomed by *B. multicinctus* (paper II)

A total of 60 consecutive cases admitted to the PCC in Hanoi during the 4-year study period for the treatment of envenoming by *B. multicinctus* were collected. Forty-six patients were male (77%) and 14 were female. Their mean age was 33.3 ± 13.5 years, ranging from 12 to 67 years. The most common occupational category among the patients were agricultural workers (57%).

Most commonly the attack took place either at home or in the rice field (Table 16). The majority of the snakebites occurred during the night-time (Fig. 7). Thus, the snake was recognized in only 38 patients (63%). The body parts most commonly bitten were the hands and feet.

Table 16. Site of the snake attack (n=60).

Site	n (%)
Home	21 (35)
Rice field	20 (33)
Village road	11 (18)
Ponds	5 (8)
Other	3 (5)

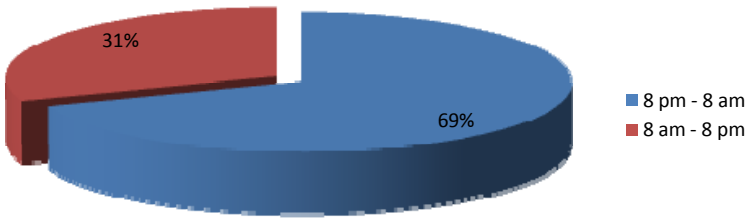

Figure 7. The time of day of the snake attack.

The mean time from the bite until the first symptom developed was 3.0 ± 3.6 hours, ranging from 0.5 to 24 hours. Most commonly the first manifestations were pharyngeal pain, ptosis, general myalgia, dyspnea, and dysphagia. According to the PSS criteria, 54 patients (90%) were classified as having severe or lethal envenomation (PSS grades 3-4), and only 3 patients (5%) displayed mild symptoms (PSS grade 1).

The clinical manifestations of the snakebite were rather specific. Not one single patient had any local symptoms such as swelling or necrosis. Fang marks were noted in 54 cases. The neuromuscular symptoms and signs most commonly observed during the stay at the ICU of the PCC were ptosis, mydriasis, ophthalmoplegia, jaw weakness, pharyngeal pain, palatal palsy, general myalgia, neck muscle paralysis, paralysis of the extremities (most pronounced proximally), absent or diminished tendon reflexes, paralysis of the respiratory muscles, urinary retention, and decreased bowel movement (Table 17).

Table 17. Neuromuscular symptoms and signs commonly recorded during the ICU stay (n=60).

Neuromuscular symptoms and signs	n (%)
Ptosis	56 (93)
Mydriasis	56 (93)
Proximal limb palsy	51 (85)
Distal limb palsy	46 (77)
Absent or diminished deep tendon reflexes	47 (78)
Ophthalmoplegia	49 (82)
Jaw paralysis	54 (90)
Palatal paralysis	54 (90)
Pharyngeal pain	50 (83)
Neck muscle paralysis	51 (85)
Diaphragmatic palsy	49 (82)
Intercostal muscle palsy	52 (87)
Dyspnea	52 (87)
General myalgia	41 (68)
Urine retention	40 (67)
Absent or decreased bowel movement	27 (45)

Respiratory failure was either a result of respiratory muscle paralysis and/or palatal paralysis leading to accumulation of secretion. The cardiovascular signs most often documented were tachycardia (defined as a heart rate faster than 100 beats per minute during > 6 hours the first two days) and hypertension (above 140/90 mmHg during > 6

hours the first 2 days). Conjunctivitis as a result of dry eyes was also commonly noted. Among the laboratory results, the most surprising was a high rate of significant hyponatremia (serum sodium level less than 130 mmol/L) (Table 18). When it occurred, this disturbance mostly developed during day 2 or day 3 after the snakebite.

Table 18. Extra-neuromuscular symptoms and signs commonly recorded during the ICU stay (n=60).

Symptoms and signs	n (%)
Tachycardia	50 (83)
Hypertension	26 (43)
Conjunctivitis	41 (68)
Corneitis	1 (2)
Hyponatremia	25 (42)

The most commonly recorded complication was ventilator-associated pneumonia due to long-term mechanical ventilation; this was observed in 37 patients (62%). Other important complications documented were infection of the urinary tract (23 cases) and ileus (2 cases). No antivenom was available during the study period. Supportive care, especially mechanical ventilation, was therefore the main treatment given. Fifty-two of the patients in the study population had to be endotracheally intubated for this purpose. The duration of artificial ventilation averaged 8.2 ± 7.3 days, ranging from 1 to 29 days. A majority of the patients were also treated with antibiotics and sodium replacement as well as local ophthalmologic therapy (Table 19).

Table 19. The ICU management of the 60 envenomed patients.

Treatments commonly given	n (%)
Endotracheal intubation	52 (87)
Tracheotomy	2 (3)
Mechanical ventilation	52 (87)
Antibiotic therapy	40 (67)
Extra sodium replacement	40 (67)
Ophthalmologic therapy (vitamin A, antibiotics)	48 (80)

The mean duration of the ICU stay in the study population was 12 ± 9 days, ranging from 1 to 36 days. The hospital mortality rate was 7%. All 4 patients died in the ICU. Two of them died in connection with their admission to the ICU, another because of malfunction of a ventilator, and the fourth died of severe hyponatremia-induced brain damage. In addition, two patients suffered long-term sequelae. One had an anoxic brain injury and another became dependent on a tracheostomy cannula.

4.2.2 Efficacy of a novel antivenom in patients envenomed by *B. multicinctus* (Paper III)

During the 3-year study period, a total of 81 patients fulfilled the inclusion criteria and entered the controlled clinical trial. Of these, 54 patients were included during the years 2004 and 2005 (control group) and 27 during 2006 (antivenom group). The baseline characteristics were similar in the two groups, and are presented in Table 20. Most patients were male and of a productive age. Children below the age of 15 years represented 14% of the study population, and elderly patients (>60 years) accounted for 4%. Most of the patients developed their first symptoms within approximately 3 hours after the snakebite, and were admitted to the ICU later than 6 hours after the bite. All included patients displayed moderate or severe envenomation on admission according to the PSS criteria, with similar severity in the two groups.

Table 20. Baseline characteristics in the two study groups.

Variables		**Control group**	**Antivenom group**	**Significance**
Age (years)		34 ± 15	36 ± 17	NS
Sex				NS
	Male	38 (70%)	18 (67%)	
	Female	16 (30%)	9 (33%)	
Time to development of first symptom (hours)		3.1 ± 2.7	2.7 ± 1.9	NS
Duration from snakebite to admission (number of patients)				NS
	Within 6 hours	13 (24%)	9 (33%)	
	> 6 hours	41 (76%)	18 (67%)	
Site of bite				NS
	Limb	49 (91%)	25 (93%)	
	Trunk	3 (6%)	1 (4%)	
	Unknown	2 (4%)	1 (4%)	
Severity score on recruitment				NS
	Moderate (PSS 2)	9 (17%)	4 (15%)	
	Severe (PSS 3)	45 (83%)	23 (85%)	

NS = not significant; PSS = Poisoning Severity Score[12]

The time span between the snakebite and the start of antivenom therapy was 19 ± 9 hours, ranging from 5 to 38 hours. Twenty patients were treated by antivenom within 24 hours after the bite (only 2 patients within 6 hours). The average dose of administered antivenom was 8.1 ± 3.2 ampoules, ranging from 5 to 17 ampoules.

The patients in the antivenom group had a significantly shorter duration of paralysis of the extremities, the diaphragm, and of ptosis. Hyponatremia was a common finding in the study population. The proportion of patients with marked hyponatremia (serum sodium level of less than 130 mmol/L) was somewhat lower in the antivenom group, and severe hyponatremia (sodium level <120 mmol/L or symptomatic) was only observed in the control group (2 patients). The rate of ventilator-associated pneumonia was significantly lower in the antivenom group (Table 21).

Table 21. A comparison between the two groups regarding some clinical findings during the stay in the intensive care unit.

Clinical findings	**Control group**	**Antivenom group**	**Significance (p)**
Duration of limb paralysis (days)	7.5 ± 6.9	2.2 ± 2.6	<0.001
Duration of diaphragm palsy (days)	7.0 ± 7.0	1.6 ± 1.6	<0.001
Duration of ptosis (days)	6.3 ± 4.7	3.5 ± 1.5	<0.001
Hyponatremia with serum Na <130 mmol/L (number of patients)	27 (50%)	9 (33%)	0.16
Ventilator-associated pneumonia (number of patients)	27 (50%)	6 (22%)	0.02

Table 22 presents the treatment measures in the two groups. There was no fatality. The relative numbers of patients requiring endotracheal intubation and mechanical ventilation were similar in the two groups. However, the duration of mechanical ventilation and endotracheal intubation, and the length of the ICU stay were significantly shorter in the antivenom group. No treatment with any cholinesterase inhibitor was given during the 3-year study period.

In the seven patients treated with antivenom later than 24 hours after the snakebite, the duration of mechanical ventilation and the length of the ICU stay were longer than those in the 20 patients who received antivenom within 24 hours (Mann-Whitney test, p values 0.07 and 0.01, respectively).

No patient in the study developed severe acute anaphylaxis. The rate of adverse reactions was 7.4% (2/27). A moderate allergic reaction in the form of urticaria was noted in one patient. Liver transaminase levels were transiently increased in another patient, in whom the maximum values of aspartate transaminase (AST) and alanine transaminase (ALT) were observed on the fifth day (344 and 442 U/L, respectively, or approximately 10 times the upper reference levels). Serum sickness was not observed in the study. Among the patients in the control group, none developed any allergic reaction and none had significantly but transiently elevated liver enzymes.

Table 22. A comparison between the two groups regarding some treatment measures during the intensive care unit (ICU) stay.

Outcome measures	**Control group**	**Antivenom group**	**Significance (p)**
Duration of mechanical ventilation (days)			<0.001
Mean (±SD)	8.6 ± 8.1	2.3 ± 2.5	
Range	0 - 31	0 - 12	
Duration of intubation (days)			<0.001
Mean (±SD)	10.1 ± 9.3	3.0 ± 2.6	
Range	0 - 40	0 - 12	
Length of ICU stay (days)			<0.001
Mean (±SD)	11.6 ± 9.7	6.1 ± 3.2	
Range	1 - 46	1 - 15	
Number of patients requiring mechanical ventilation	44 (81.5%)	23 (85.2%)	NS

NS = not significant.

5 DISCUSSION

5.1 FREQUENCY, CHARACTERISTICS AND MANAGEMENT OF POISONING EMERGENCIES (PAPER I)

The annual number of admitted cases of poisoning increased rapidly during the initial years of the first PCC in Vietnam. Similar findings were reported from Thailand during the same period [3], and probably reflect an increasing awareness of the existence of the PCC among members of the medical society and the population at large. Another explanation may be an increasing awareness of the need of specialized care of these emergencies.

The study result established that the clearly most common location of the toxic exposures was the patient's home. This finding may provide a basis for intervention measures and steps towards an improved poisoning prevention strategy in Vietnam.

Among underlying toxic agents, the heterogeneous group "food poisoning" was found to be the most frequent. Pharmaceuticals constituted the second most common group, in conformity with the general pattern of poisoning in the USA and Europe, as well as in developing countries [2, 68]. In Vietnam, medications are readily accessible as a consequence of a lack of regulations, which is a great problem, especially concerning suicidal patients and children. This fact constitutes another important issue for the health care system and the government in Vietnam to consider in their attempts to prevent poisoning.

Pesticides have been identified as the agents responsible for a majority of deaths from poisoning in developing countries [3, 29]. A study in Zimbabwe showed that pesticides accounted for the largest proportion of deaths from poisoning at both district and provincial hospitals, indicating that mortality from pesticides is a problem both in urban and rural areas [69]. In a study in Sri Lanka it was found that easily available pesticides in rural areas, economic problems and family conflicts were the main underlying causes of intentional pesticide poisoning [70]. In the present study, pesticides were responsible for many fatalities and were the chemicals most frequently used by patients from rural areas. This implies that pesticide poisoning should be given special attention and requires intervention measures from health care givers and responsible persons in the community.

Envenomation was the most common cause of poisoning of natural origin and snakebite was the dominating cause in this group. The snakes in northern Vietnam are numerous and some kinds are very poisonous. The magnitude of this problem has also been highlighted from other countries [69, 71, 72].

The clinical features included respiratory failure, and approximately 8% of the poisoned patients required intubation and mechanical ventilation. Similar findings have been reported from Turkey [73]. The rate of decontaminating interventions such as gastric lavage and administration of cathartics in the present study was higher than that recently reported [74] and recommended [75] from countries in Europe and the USA. However, the rate of antidote treatment was low, probably mainly on account of poor access in Vietnam to these often expensive pharmaceuticals.

The mortality rate in the present study was low compared to reports from some other developing countries [3, 29, 69, 72]. Similar mortality rates of approximately 1% have been reported, however, from Turkey [76, 77] and Iran [78]. Countries with high mortality rates have often also reported a high frequency of intake of very toxic agents, such as aluminum phosphide in a study from India [29], and paraquat in a study from Thailand [3].

5.2 POTENTIALLY HAZARDOUS ENVIRONMENTAL FACTORS FOR POISONING IN RURAL VIETNAM (PAPER IV)

The major finding was that the availability and accessibility of pesticides constitute the main risk factor for poisoning among ordinary people in rural parts of Vietnam. This is partly explained by the fact that many kinds of highly toxic insecticides, herbicides, and rodenticides are widely spread and commonly used in Vietnam, and partly by the lack of effective control regulations and strategies to reduce this threat to public health. Acute poisoning by agricultural pesticides is a well established public health problem in developing countries, with an estimated 300,000 deaths annually worldwide [79]. Previous scientific reports have suggested that the widespread availability of pesticides in rural communities is a crucial risk factor in a majority of all fatal self-poisonings [80, 81]. Easy accessibility of pesticides to adults and children is also a reality in many other developing countries such as Sri Lanka and China [82, 83]. This fact requires a prompt poisoning-prevention approach to reduce the availability of pesticides, especially those that are most toxic.

A second finding was that another important source of toxins in the rural area of Vietnam is its poisonous flora and fauna. The hazardous habit of ingesting and otherwise using unusual and unknown herbs reflects the fact that remedies and traditional medicine are popular in this area and that many Vietnamese people do not believe that herbs are toxic. The lack of necessary public information and control regulations makes the situation worse. This is an important problem not only in many Asian countries but also in other parts of the world [82, 84]. The belief that ingestion of some poisonous animals is good for health has resulted in the fact that many households raise venomous snakes for economic reasons, and life-threatening envenomations are not uncommon in Vietnam [85].

Another risk factor for poisoning recorded in this study was the availability and inadequate storage of hazardous household products. Such products were commonly within reach of children and were sometimes stored in beverage bottles, thereby constituting a risk for unintentional poisoning. This finding is consistent with previous reports from other regions [3, 86, 87].

Self-medication, through retail pharmacies without professional consultation, was commonly reported in this study. The problem of drug utilization and self-medication in Vietnam has been reported previously [88]. In a recently published hospital-based study on poisoning in Vietnam [89], pharmaceutical overdose was recorded as one of the most common types of acute poisoning.

5.3 CLINICAL FEATURES OF 60 PATIENTS ENVENOMED BY *B. MULTICINCTUS* (PAPER II)

This study involves the largest number of patients severely envenomed by *B. multicinctus* reported in the literature so far. A few case series and epidemiologic studies have previously been reported, however, from the Southeast Asian region [54, 55], Taiwan [90], and the south of China [56]. The major findings in this study were the high proportion needing mechanical ventilation and the high rate of acute hyponatremia. The study population was, of course, highly selected, as all patients were admitted to an ICU, but 54 severe cases from the area surrounding Hanoi during a 4-year period definitely implies a grave prognosis if untreated.

In accordance with other case series, the bite by *B. multicinctus* was found to occur commonly in rural areas, where the habitats of snakes overlap with the human

environment [54, 90]. Thus, agricultural workers clearly predominated among the victims. As also noted for other krait species such as *B. caeruleus* and *B. candidus* [62, 91], the attacks of *B. multicinctus* usually occur during the night-time [54, 55]. The most common locations of the attacks in our study, the patients' homes and the rice field, are rather similar to those reported in other case series [55, 90].

In previously reported *B. multicinctus* envenoming, the first neurological symptoms developed within a few hours after the bite [54, 55], and in envenoming by other krait species, they appeared within 12 hours [62, 92]. In the present study the first symptoms developed within a wide time-range of 0.5 to 24 hours. This should be considered regarding the duration of observation required in these patients.

The neuromuscular symptoms and signs recorded in this study were in conformity with those described in previous case series of envenoming by *B. multicinctus* [54, 55], as well as by some other kraits [91-93]. Ptosis and ophthalmoplegia were frequently observed and often led to dry eyes and conjunctivitis, or even corneitis in one case. These events are important to recognize and require particular nursing cautions. Mydriasis was also recorded in a clear majority of the patients. The dilatation of the pupils was often maximal and was extremely persistent in some cases (Fig. 3). The commonly documented palatal paralysis with inability to swallow was one of the reasons for respiratory failure in the early phase of the ICU course, but was also a cause of extubation failure in some cases in the late phase. This should be carefully considered, concomitantly with respiratory muscle palsy in the respiratory management of these cases. The most severely affected patients developed generalized muscle paralysis and became completely unresponsive. This situation, combined with apnea and dilated pupils, may easily be misdiagnosed as brain death. Electroencephalography and nerve conduction studies therefore may be indicated in situations of uncertainty.

The envenomed patients in the study often experienced general myalgia (Table 4). Some patients still had pain and numbness several months after discharge, requiring analgesic therapy. This phenomenon resembles the case of peripheral sensory neuropathy after a krait bite reported from Sri Lanka [92].

Tachycardia and hypertension were noted in many patients. These findings have been reported previously after snakebite by *B. multicinctus* [54] and also by another krait species, namely *B. candidus* [94]. It has been suggested that these clinical features may

be due to a decreased parasympathetic tone and may be treated with beta adrenergic blockers [94].

The important finding of a rapidly developing significant hyponatremia in nearly half of the present study population was surprising. This electrolyte disturbance has not been reported previously after envenoming by *B. multicinctus*. We do not know the exact mechanism of the disturbance, but the sodium content of the urine was found to be elevated in a majority of the cases. Hyponatremia has been reported also following bites by the American coral snake, *B. flaviceps* and some other snakes. The mechanism underlying the electrolyte disturbance after that snakebite was reported to be a natriuretic peptide in the venom [95-97]. We strongly recommend that serum electrolyte levels be followed up in every patient envenomed by *B. multicinctus*, and that sodium be replaced immediately if necessary.

Fifty-two patients or 87% of the study population needed mechanical ventilation. This finding emphasizes the seriousness of snakebite from this particular species. The duration of the artificial ventilation in our study was longer than that in a study from India describing severe neuroparalytic pulmonary status after different snake envenomations [98]. The recorded hospital mortality rate of 7% in our study, despite ICU treatment, also underlines the danger of envenoming by *B. multicinctus*.

5.4 EFFICACY OF A NOVEL ANTIVENOM IN PATIENTS ENVENOMED BY *B. MULTICINCTUS* (PAPER III)

The major findings in this controlled clinical trial were the favourable clinical efficacy of the tested antivenom and the lack of severe adverse reactions to this treatment. The significant results of the study were achieved despite the fact that 93% of the patients in the interventional group received the antivenom therapy more than six hours after the snakebite.

Although an improvement of most tested symptoms was demonstrated in the antivenom group in the present study, the relative number of patients requiring mechanical ventilation was not reduced. The considerable delay before ICU admission is the likely explanation. The reason why some patients had to stay endotracheally intubated also after they had been weaned from the ventilator (Table 3), was that a palatal paralysis with inability to swallow sometimes persisted longer than the paralysis of the respiratory muscles.

A high rate of hyponatremia was observed in the study population as was also reported in a previous study on snakebite by this particular species.

The average dose of the antivenom used in the present study was similar to the dose regimen used in a study in China, and in accordance with the recommended doses of other antivenom products used against bites by this *Bungarus* species [56]. With the aim of protecting its stability, the antivenom was not diluted in large amounts of solution in our study, but nevertheless was infused slowly during a period of one hour. Since skin testing is today not only considered unnecessary but also misleading, and pretreatment with antihistamine, epinephrine or corticosteroids is controversial, neither a skin test nor any pretreatment was performed in the present study [99-102].

The reported frequencies of adverse reactions after different types of antivenom therapies have varied considerably. Acute reactions in 23-56% of the patients and high frequencies of serum sickness (up to 75%) have been recorded, but in other studies the rates of these complications have been rather low or approximately 10% [58, 103-105]. The main explanation for this discrepancy is that the older immunoglobulin-based antivenoms had several side effects, whereas more recent, purer equine antivenoms, containing $F(ab')_2$ or Fab fragments, produce few side reactions [59]. In our study, no severe reactions were recorded and a single moderate reaction was observed in a patient who developed urticaria. This was probably due to the high quality of the $F(ab')_2$ antivenom in combination with rational dosing and slow administration. The transiently increased level of transaminases observed in another patient may possibly have had another, unknown explanation.

6 CONCLUSIONS

- The hospital-based retrospective study of poisoning emergencies in Hanoi (Paper I) showed that a vast majority of the poisoning episodes occurred at home. This is important knowledge for the poisoning prevention efforts in the country. Moreover, the fact that hypnotic pharmaceuticals, heroin and pesticides were among the most commonly involved toxic agents and that they entailed an increased risk of a fatal outcome, show that more strict regulation of these potential toxins is crucial. Finally, the frequently recorded severe toxic symptoms, including coma, respiratory failure, hypotension and seizures, indicate a need for more specialized clinical poisoning units with intensive care facilities in Vietnam.

- The cross-sectional community-based study from a rural part of Vietnam (Paper IV) pointed out that the availability and accessibility of pesticides constitute the main risk factor for poisoning among ordinary people in Vietnam. A second important source of toxins in the rural area of Vietnam is its poisonous flora and fauna. Other common risk factors for poisoning were the availability and inadequate storage of hazardous household products and self-medication, through retail pharmacies without professional consultation.

- The study of 60 consecutive ICU-treated patients envenomed by B. *multicinctus* (Paper II) demonstrated that bites by *B. multicinctus* commonly occur in rural areas and during night-time. The first symptoms developed within a wide time-range of 0.5 to 24 hours. The dilatation of the pupils was often maximal and extremely persistent in some cases. A majority of the patients developed generalized muscle paralysis. Eighty-seven percent of the study population needed mechanical ventilation. The new finding of a high rate of significant hyponatremia makes frequent laboratory monitoring and sometimes prompt sodium replacement imperative, and the severe clinical features recorded indicate an urgent need for a specific antivenom.

- The controlled clinical trial of a novel antivenom against *B. multicinctus* (Paper III) clearly demonstrated its favourable efficacy and acceptable safety. The prospective study also confirmed the new finding in paper II of a high risk for development of significant hyponatremia after snakebite by this particular species.

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I

THE FIRST POISON CONTROL CENTER IN VIETNAM: EXPERIENCES OF ITS INITIAL YEARS

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Abstract**.** Poisoning is a sparsely studied but major health problem in Vietnam. In this hospital-based retrospective study, the medical records of all cases of poisoning admitted to the Poison Control Center in Hanoi from 1999 to 2003 were carefully reviewed. A total of 1,836 poisoning emergencies were recorded. The female:male ratio was approximately 1:1. The largest number of poisoned patients was found in the age-group 15-24 years. A vast majority of the toxic exposures (74.1%) occurred at the patients' homes. Suicidal poisoning constituted about one third of all cases. The most commonly involved toxic agents consisted of the heterogeneous group "food poisoning" (35.1%), pharmaceuticals (33.8%), toxins from poisonous animals, mostly snake bites (12.6%), and pesticides (9.1%). On admission, two thirds of the patients had mild symptoms (Poisoning Severity Score, PSS grade 1), while more than a quarter displayed pronounced clinical signs of poisoning (PSS grades 2-4). The most frequently used poisoning-specific treatments were gastric lavage (30.2%) and administration of activated charcoal (35.4%) and cathartics (34.2%). Intensive care measures, such as mechanical ventilation and dialysis, were applied less frequently, in 6.5% and 1.7%, respectively. Specific antidotes were given in 5.2% of the cases. The total number of fatalities was 21 (1.1%) and 10 patients were discharged with a neurological sequela. Hypnotic pharmaceuticals (mainly barbiturates), heroin, and pesticides were involved in a majority of the fatalities. These data provide an important basis for poisoning prevention efforts in developing countries such as Vietnam.

INTRODUCTION

Poisoning is a common cause of medical emergencies and a threat to public health. In the year 2000, poisoning was the ninth most common cause of death in young adults worldwide and there were more than three million cases of poisoning, with a mortality rate of approximately 8% (Peden *et al*, 2002). It has been estimated that over 90% of such fatalities occur in developing countries (Peden *et al*, 2002).

Vietnam is a developing country with approximately 84 million inhabitants. Its population is relatively young, 39% consisting of children and adolescents, while 17% are elderly (Vietnam National Health Report 2006). In general Vietnam is an agricultural country and farmers account for nearly 75% of the population, creating a large market for biocides and other toxic chemicals. As a result of the ready availability of poisons and the lack of an effective control strategy, poisoning has become a major health problem throughout the country. However, reliable data on poisoning patterns in Vietnam are sparse and incomplete, and to our knowledge no study on clinical toxicological issues from this country has been published previously in any international medical journal.

The first Poison Control Center in Viet-

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nam (PCC) was started at Bach Mai Hospital in Hanoi in 1998. The PCC consists of four units: a clinical department with 20 beds and intensive care facilities, a toxicological laboratory, a poison information unit, and an antivenom research unit.

The aim of the present study was to investigate the poisoning patterns in northern Vietnam and also the frequency and characteristics of poisoning emergencies admitted to the clinical department of the PCC in Hanoi during its first five years, with special focus on a comparison of the years 1999 and 2003.

MATERIALS AND METHODS

In this retrospective study, the medical records of all patients admitted to the PCC between the years 1999 and 2003 because of poisoning were carefully reviewed.

Poisoning was defined as drug overdose, food poisoning, or exposure to any environmental toxic substance. A study protocol was developed from the existing IPCS-Case/Incident/Request Format (http://www.who.int/ipcs/poisons/Minform-Eng.XLS). The protocol was subsequently refined and covered all pertinent data including demographics, type of poisoning, clinical findings, treatment, and outcome.

The patients either presented directly to the PCC or were referred from other hospitals in northern Vietnam. The severity of each case of poisoning was defined upon admission, using the 5-graded Poisoning Severity Score (PSS) criteria of the IPCS (Persson *et al*, 1998).

The outcome for each patient was classified into one of three categories: 1. recovery, 2. sequela (an impairment of functioning corresponding to a performance category of 2-4 on the 5-graded Glasgow-Pittsburgh Outcome Scale (Jannett and Bond, 1975; Cummins *et al,* 1991) on discharge from hospital), or 3. death during hospitalization.

The chi-square test was used for statistical calculations, and differences were considered significant if the p-value was <0.05.

RESULTS

The annual total number of patients admitted to the clinical department of the PCC increased during the five-year period 1999-2003 (Fig 1). However, patients with other diagnoses than poisoning were also treated in the department, especially during its first few years, when the existence of the PCC was not very well known either to the population or to the medical community of Hanoi.

In 1999 the number of patients with poisoning admitted to the PCC was 313 (59.5% of the total number of admissions) and in 2003 the corresponding number was 1,523 (91.3% of the total number of admissions). In 1999,

Table 1
Occupational distribution of the poisoned patients for the years 1999 and 2003.

Occupation	1999, *n*=313	2003, *n*=1,523	Total, *n*=1,836	
	n	*n*	*n*	%
Service occupation	57	474	531	28.9
Student	54	358	412	22.4
None	85	256	341	18.6
Agricultural worker	82	250	332	18.1
Industrial worker	24	160	184	10.0
Other or unknown	11	20	36	2.0

Table 2
Location of toxic exposures during the years 1999 and 2003.

Location of exposure	1999, *n*=313	2003, *n*=1,523	Total, *n*=1,836	
	n	*n*	*n*	%
Home	266	1,094	1,360	74.1
Public space	14	102	116	6.3
Restaurant	1	95	96	5.2
Workplace	13	43	56	3.1
Rented house	2	18	20	1.1
Transport facility	2	12	14	0.8
Medical facility	6	9	15	0.8
Other or unknown	9	150	159	8.7

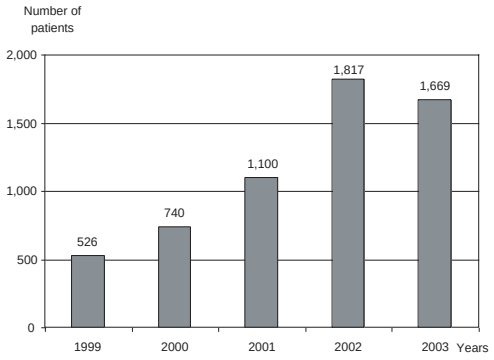

Fig 1–The total numbers of patients admitted to the first Poison Control Center (PCC) in Vietnam during the years 1999-2003.

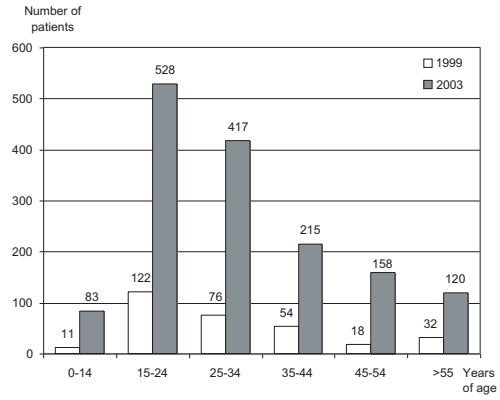

Fig 2–Age distribution of the poisoned patients treated in the PCC during 1999 and 2003.

females accounted for 54.3% of the poisonings, and in 2003 this figure was 48.5%. The largest number of poisoned patients was found in the age-group 15-24 years. The youngest patient treated during these two years was 23 months old and the oldest was 96 years old (Fig 2).

The occupational distribution of the admitted cases of poisoning is presented in Table 1. In the year 1999, unemployed persons and agricultural workers were the most common occupational groups among the poisoned patients. Four years later, students and people working in service occupations increased dramatically.

A finding that did not change during the 5-year period was that a vast majority of the toxic exposures occurred at home (Table 2).

Concerning the types of toxic agents causing the poisoning, the most common in 1999 were pharmaceuticals and pesticides. In 2003 food poisoning predominated, followed by pharmaceuticals, toxins from poisonous animals (mostly snake venom), and pesticides (Table 3). The pesticides were a miscellaneous mixture of toxic chemicals, but consisted mainly of insecticides such as organophosphates, carbamates, organochlorines, or pyrethroids, or rodenticides, such as sodium

Table 3
Types of toxic agents involved in the cases of poisoning.

Type of toxin	1999, *n*=313	2003, *n*=1,523	Total, *n*=1,836	
	n	*n*	*n*	%
Food/beverages	19	626	645	35.1
Pharmaceuticals	160	460	620	33.8
Poisonous animals (mostly snakes)	29	202	231	12.6
Pesticides (including rodenticides)	61	107	168	9.2
Drug abuse (heroin)	13	72	85	4.6
Household/leisure products	6	12	18	1.0
Industrial / commercial products	8	7	15	0.8
Environmental contamination	1	9	10	0.5
Plants	3	6	9	0.5
Other or unknown	13	22	35	1.9

Table 4
Routes of exposure among the poisoned patients during the years 1999 and 2003.

Route of exposure	1999, *n*=313	2003, *n*=1,523	Total, *n*=1,836	
	n	*n*	*n*	%
Ingestion	269	1,190	1,459	79.5
Bite	28	133	161	8.8
Sting	0	64	64	3.5
Injection	8	53	61	3.3
Inhalation	5	29	34	1.9
Cutaneous	0	7	7	0.4
Other or unknown	3	47	50	2.7

Table 5
Intentional versus unintentional poisoning.

Circumstance of exposure	1999, *n*=313	2003, *n*=1,523	Total, *n*=1,836	
	n	*n*	*n*	%
Unintentional (accidental)	82	823	905	49.3
Intentional-suicide	178	393	571	31.1
Intentional-misuse, abuse, malicious	34	234	268	14.6
Unknown	19	73	92	5.0

monofluoroacetate, zinc phosphide or anticoagulant agents.

The clearly predominating route of exposure was ingestion. Bites and stings from poisonous animals were also relatively common. Injection of heroin and inhalation of toxic gases were examples of less common routes of exposure (Table 4).

Compared with accidental toxic exposures, the number of deliberate poisonings

Table 6
Poisoning Severity Score (PSS) on admission to the PCC.

Severity of poisoning (PSS)	1999, *n*=313	2003, *n*=1,523	Total, *n*=1,836	
	n	*n*	*n*	%
None (0)	58	77	135	7.4
Minor (1)	163	1,051	1,214	66.1
Moderate (2)	39	259	298	16.2
Severe (3)	53	135	188	10.2
Fatal (4)	0	1	1	0.1

Table 7
The distribution of specified poisoning-induced symptoms recorded at the PCC.

Poisoning-induced symptoms	1999, *n*=313	2003, *n*=1,523	Total, *n*=1,836	
	n	*n*	*n*	%
Reduced level of consciousness[a]	83	235	318	17.3
Respiratory failure	64	83	147	8.0
Hypotension (systolic BP <90 mm Hg)	33	96	129	7.0
Rhabdomyolysis	12	111	123	6.7
Seizures	15	73	88	4.8
Bradycardia (heart rate <50)	5	28	33	1.8
Ventricular arrhythmia[b]	13	19	32	1.7
Acute renal failure	10	18	28	1.5
Acute hepatic failure	3	16	19	1.0
Gastrointestinal hemorrhage	2	15	17	0.9

[a]Glasgow Coma Scale score <13
[b]Including 26 patients with frequent ventricular extrasystoles and 6 with ventricular tachycardia.

was larger in 1999 and smaller in 2003. In total, these two types of the toxic exposure were approximately equally common. Suicidal poisoning constituted approximately one third of all cases of poisoning (Table 5).

A majority of the poisoned patients displayed mild symptoms (PSS grade 1) on admission to the PCC. However, more than a quarter of the total number of poisoned patients showed pronounced clinical signs of poisoning and some had life-threatening symptoms. During the year 1999, the relative proportion of patients with severe poisoning (PSS grades 3-4) was higher than during 2003 (16.9% and 8.9%, respectively, p<0.001) (Table 6).

The occurrence of specified poisoning-induced symptoms recorded during the hospital stay is shown in Table 7. The most common signs of serious poisoning were a reduced level of consciousness, respiratory failure, hypotension, rhabdomyolysis, and seizures.

The poisoning-specific treatments most commonly used during the study years were decontamination measures, such as administration of cathartics, activated charcoal, gastric lavage and skin decontamination. Intensive care measures, such as mechanical ventilation and dialysis, were used less frequently. Specific antidotes were given in approximately 5% of all cases (Table 8).

Table 8
Use of therapeutic interventions in the poisoned patients at the PCC.

Treatment	1999, *n*=313	2003, *n*=1,523	Total, *n*=1,836	
	n	*n*	*n*	%
Induced emesis	12	71	83	4.5
Gastric lavage	191	364	555	30.2
Charcoal, single dosage	143	437	580	31.6
Charcoal, repeat dosages	46	25	71	3.9
Cathartic	195	433	628	34.2
Skin decontamination	23	66	89	4.8
Irrigation of eye	4	12	16	0.9
Endotracheal intubation	64	83	147	8.0
Mechanical ventilation	56	64	120	6.5
Antidote administration	16	80	96	5.2
Hemodialysis	8	23	31	1.7

Table 9
Main outcomes among the cases of poisoning at the PCC.

Main outcome	1999, *n*=313	2003, *n*=1,523	Total, *n*=1,836	
	n	*n*	*n*	%
Recovery	306	1,499	1,805	98.3
Sequela	1	9	10	0.5
Fatal	6	15	21	1.1

The mean stay in the PCC was 2.10 ± 0.99 days. Of the total of 1,836 poisoned patients, 1,322 (72.1%) were discharged within 24 hours. However, 140 patients (7.6%) required hospitalization for more than one week. The longest treatment duration was 62 days.

The main outcomes among the poisoned patients treated at the PCC during 1999 and 2003 is shown in Table 9. The hospital mortality rate was higher in 1999 (1.9%) than in 2003 (1%), but the difference was not statistically significant. The fatalities mainly resulted from poisoning by hypnotic pharmaceuticals (phenobarbital in 5 cases), heroin overdose and some very toxic pesticides (Table 10).

DISCUSSION

The annual number of admitted cases of poisoning increased rapidly during the initial years of the first PCC in Vietnam. Similar findings were reported from Thailand during the same period (Wananukul *et al*, 2007), and probably reflect an increasing awareness of the existence of the PCC among members of the medical society and the population at large. Another explanation may be an increasing awareness of the need of specialized care of these emergencies.

From studies in Turkey, the female-to-male ratio of poisoning-related emergencies was reported to be 3:1. A majority of the poisoned patients in that country were younger than 25 years of age (Özköse and Ayoğlu, 1999; Tüfekçi *et al*, 2004). Studies in Malaysia (Fathelrahman *et al*, 2005) and India (Singh and Unnikrishnan, 2006) also showed approximately the same demographic characteristics

Table 10
Toxic agents associated with the fatalities.

Toxic agents	Number of fatalities		Total number of fatalities/No. of cases	Case fatality rate (%)
	1999	2003		
Hypnotic pharmaceuticals	3	4	7/382	1.8
Heroin		5	5/85	5.9
Pesticides	1	3	4/168	2.4
Herbal medicines		2	2/29	6.9
Hydrochloric acid	1		1/15	6.7
Cyanide	1		1/15	6.7
Snake venom		1	1/163	0.6

of poisoned patients. In the present study, the female-to-male ratio was almost 1:1. The higher rate of unintentional poisonings in this study may explain the difference.

The present study found the most common location for toxic exposures was the patient's home. This finding may provide a basis for intervention measures and steps towards an improved poisoning prevention strategy in Vietnam.

Among underlying toxic agents in this study, the heterogeneous group "food poisoning" was found to be the most frequent. Pharmaceuticals constituted the second most common group, in conformity with the general pattern of poisoning in the USA and Europe, as well as in developing countries (Hanssens *et al*, 2001; Fathelrahman *et al*, 2005). In Vietnam, medications are readily accessible as a consequence of a lack of regulations, which is a great problem, especially concerning suicidal patients and children. This fact constitutes another important issue for the health care system and the government in Vietnam to consider in their attempts to prevent poisoning.

Pesticides have been identified as the agents responsible for a majority of deaths from poisoning in developing countries (Singh and Unnikrishnan, 2006; Wananukul *et al*, 2007). A study in Zimbabwe showed that pesticides accounted for the largest proportion of deaths from poisoning at both district and provincial hospitals, indicating that mortality from pesticides is a problem both in urban and rural areas (van der Hoek and Konradsen, 2006). In a study in Sri Lanka it was found that easily available pesticides in rural areas, economic problems and family conflicts were the main underlying causes of intentional pesticide poisoning (Eddleston *et al*, 2006). In the present study, pesticides were responsible for many fatalities and were the chemicals most frequently used by patients from rural areas. This implies that pesticide poisoning should be given special attention and requires intervention measures from health care givers and responsible persons in the community.

Envenomation was the most common cause of poisoning of natural origin in this study and snakebite was the dominating cause in this group. The snakes in northern Vietnam are numerous and some kinds are very poisonous. The magnitude of this problem has also been highlighted from other countries (Batra *et al*, 2003; Tagwireyi *et al*, 2006; van der Hoek and Konradsen, 2006).

The clinical features recorded in this study included respiratory failure, and approximately 7% of the poisoned patients required

intubation and mechanical ventilation. Similar findings have been reported from Turkey (Goksu *et al*, 2002). The rate of decontaminating interventions, such as gastric lavage and administration of cathartics, in the present study was higher than that recently reported (Chyka and Winbery, 2006) and recommended (AACT and EAPCCT, 2004) from countries in Europe and the USA. However, the rate of antidote treatment was low, probably due to poor access in Vietnam of these often expensive pharmaceuticals.

The mortality rate in the present study was low compared to reports from some other developing countries (Singh and Unnikrishnan, 2006; Tagwireyi *et al*, 2006; van der Hoek and Konradsen, 2006; Wananukul *et al*, 2007). Similar mortality rates of approximately 1% have been reported, however in Turkey (Tüfekçi *et al*, 2004; Mert and Bilgin, 2006) and Iran (Afshari *et al*, 2004). Countries with high mortality rates have often reported a high frequency of intake of very toxic agents, such as aluminum phosphide in a study from India (Singh and Unnikrishnan, 2006), and paraquat in a study from Thailand (Wananukul *et al*, 2007).

In conclusion, despite the hospital-based retrospective design of this study, we consider that the data obtained provide important information on the pattern of poisonings in northern Vietnam. The finding that a vast majority of the poisoning episodes occurred at home is of importance for the poisoning prevention efforts in the country. Moreover, the fact that hypnotic pharmaceuticals, heroin and pesticides were among the most commonly involved toxic agents and that they entailed an increased risk of a fatal outcome, show that more strict regulation and control of these potential toxins is crucial. Finally, the frequently recorded severe toxic symptoms, including coma, respiratory failure, hypotension and seizures, indicate a need for more specialized clinical poisoning units with intensive care facilities in Vietnam.

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II

CLINICAL FEATURES OF 60 CONSECUTIVE ICU-TREATED PATIENTS ENVENOMED BY *BUNGARUS MULTICINCTUS*

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Abstract. In northern Vietnam, *Bungarus multicinctus* is the only krait of medical importance. We report 60 consecutive patients admitted to an ICU in Hanoi during 2000-2003 because of envenoming by *B. multicinctus*. Their mean age was 33 years (range 12-67), 77% were male. The majority were agricultural workers, 69% of the snakebites occurred during the night. The mean length of time until the first symptom developed was 3 hours (range 0.5-24 hours). The only sign at the site of the bite was fang marks, which were noted in 90%. The most common neuromuscular symptoms were ptosis and mydriasis (93%), ophthalmoplegia (82%), jaw weakness (90%), pharyngeal pain (83%), palatal palsy (90%), neck muscle paralysis (85%), limb paralysis (85%), and paralysis of the respiratory muscles (87%). No antivenom was available. Fifty-two patients (87%) needed mechanical ventilation for a mean of 8 days. The most surprising laboratory finding was a high rate of significant hyponatremia (42%). The mean duration of the ICU stay was 12 days and the hospital mortality was 7%. According to the Poisoning Severity Score criteria, 54 patients (90%) were classified as severe or lethal envenoming.

INTRODUCTION

Bites by venomous snakes are a worldwide problem, especially in tropical regions (Cheng and Currie, 2004). In Vietnam, two snake families have poisonous members, the Elapidea and the Viperidea. The elapid snakes include, among others, the kraits represented by 12 species worldwide within the single genus *Bungarus*. The kraits are generally unagressive nocturnal animals that frequently enter rural houses. Their venom can cause severe neuromuscular blockade but do not give rise to swelling or necrosis at the site of the bite (Warrel, 1995). Envenoming by several krait species is known to cause respiratory failure and fatality (Sawai *et al*, 1992; Hung, 2004). Alpha-bungarotoxin is a postsynaptically active toxin which binds to the acetylcholine receptors and prevents binding of acetylcholine. The result is a non-depolarising type of neuromuscular blockage. Moreover, the venom also contains β and γ-gungarotoxins which act presynaptically and depress the release of acetylcholine from the nerve endings. The presence of the latter toxins explains why treatment with cholinesterase inhibitors has not been very efficient (Chan *et al*, 1995; Rowan, 2001). The clinical characteristics arising from bites from *Bungarus multicinctus* (many-banded krait, Chinese krait) have rarely been described (Chan *et al*, 1995; Pe *et al*, 1997).

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B. multicinctus are found in many Asian countries, including southern China, Taiwan, Hong Kong, and northern parts of Lao PDR, Myanmar, and Vietnam (Warrel, 1995). Along the back of this snake is a series of black to bluish-black saddle-shaped markings separated by 30-50 white bands (Fig 1). The maximum length is 1.84 meters (Chan *et al*, 1995). In northern Vietnam *B. multicinctus* is the only krait species of medical significance in humans. We report a study of consecutive patients admitted to the National Poison Control Center (PCC) at Bach Mai Hospital in Hanoi during the period 2000-2003 because of envenomation by *B. multicinctus*.

MATERIALS AND METHODS

In this retrospective study the medical records of all patients treated in the intensive care unit (1CU) of the PCC for envenoming by *B. multicinctus* during the 4-year period 2000-2003 were carefully reviewed. In a majority of cases, the type of snake was determined either at the hospital by investigation of a snake specimen brought to the PCC or by the patient in connection with the bite. In some cases the snake was never seen, however, the diagnosis was then established by the circumstances of the bite together with the presence of typical clinical features. A predetermined study protocol was developed. Pertinent data of each case were recorded, including demographics, the time and circumstances of the bite, the body parts bitten, symptoms and signs, laboratory findings, any complications, length of time spent in the ICU, and the outcome. The severity of each case was defined using a 5-grade (0-4) Poisoning Severity Score (PSS) (Persson *et al*, 1998). Treatment measures documented in the medical records, such as mechanical ventilation, were also noted.

Table 1
The occupational distribution of the study population (*N*=60).

Occupation	*n* (%)
Agricultural worker	34 (57)
Student	16 (27)
Service occupations	5 (8)
Other (one patient raised snakes for trade)	5 (8)

Table 2
Site of the snake attack (*N*=60).

Site	*n* (%)
Home	21 (35)
Rice field	20 (33)
Village road	11 (18)
Ponds	5 (8)
Other	3 (5)

RESULTS

A total of 60 consecutive cases admitted to the ICU during the study period for the treatment of envenoming by *B. multicinctus* were collected. Forty-six patients were male (77%) and 14 were female. Their mean age was 33.3 ± 13.5 years, ranging from 12 to 67 years. The most common occupational categories among the patients were agricultural workers and students (Table 1).

Most commonly the attack took place either at home or in the rice field (Table 2). The majority of the snakebites occurred at night (Fig 2). The snake was recognized by 38 patients (63%). The body parts most commonly bitten were the hands and feet (Table 3).

Immediately after being bitten, the patients often carried out different kinds of first aid measures, such as the use of traditional

Table 3
The part of the body bitten (N=60).

Body part bitten	n (%)
Hand	32 (53)
Foot	16 (27)
Leg	4 (7)
Trunk	3 (5)
Arm	2 (3)
Unknown	3 (5)

Table 4
The first symptom developed after envenomation (N=60).

Symptoms	n (%)
Pharyngeal pain	13 (22)
Ptosis	12 (20)
General myalgia	9 (15)
Dyspnea	8 (13)
Dysphagia	6 (10)
Difficulty in opening the mouth	3 (5)
General weakness	3 (5)
Blurred vision	2 (3)
Limb paralysis	1 (2)
Abdominal pain	1 (2)
Missing information	2 (3)

medicine (42%), squeezing (32%), application of a tourniquet (28%), incision (20%), or cleaning (3%). The mean time until the first symptom developed was 3.0 ± 3.6 hours, ranging from 0.5 to 24 hours. Most commonly the first manifestations were pharyngeal pain, ptosis, general myalgia, dyspnea, and dysphagia (Table 4). According to the PSS criteria, 54 patients (90%) were classified as having severe or lethal envenomation (PSS grades 3-4), and only 3 patients (5%) displayed mild symptoms (PSS grade 1).

The clinical manifestations of the snakebite were rather specific. Not one single patient had any local symptoms such as swelling or necrosis. Fang marks were noted in 54 cases. The neuromuscular symptoms and signs most commonly observed during the ICU stay were ptosis, mydriasis, ophthalmoplegia, jaw weakness, pharyngeal pain, palatal palsy, general myalgia, neck muscle paralysis, paralysis of the extremities (most pronounced proximally), absent or diminished tendon reflexes, paralysis of the respiratory muscles, urinary retention, and decreased bowel movements (Table 5).

Table 5
Neuromuscular symptoms and signs commonly recorded during the ICU stay (N=60).

Neuromuscular symptoms and signs	n (%)
Ptosis	56 (93)
Mydriasis	56 (93)
Proximal limb palsy	51 (85)
Distal limb palsy	46 (77)
Absent or diminished deep tendon reflexes	47 (78)
Ophthalmoplegia	49 (82)
Jaw paralysis	54 (90)
Palatal paralysis	54 (90)
Pharyngeal pain	50 (83)
Neck muscle paralysis	51 (85)
Diaphragmatic palsy	49 (82)
Intercostal muscle palsy	52 (87)
Dyspnea	52 (87)
General myalgia	41 (68)
Urine retention	40 (67)
Absent or decreased bowel movements	27 (45)

Respiratory failure was either a result of respiratory muscle paralysis and/or palatal paralysis leading to accumulation of secretions. The cardiovascular signs most often documented were tachycardia (defined as a heart rate faster than 100 beats per minute during >6 hours during the first two days) and hypertension (above 140/90 mmHg during >6 hours during the first two days). Conjunctivitis as a result of dry eyes

Fig 1 -*Bungarus multicinctus*.

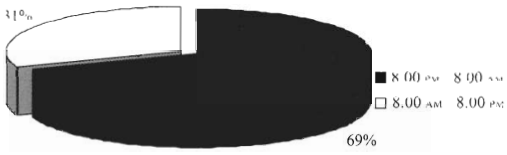

Fig 2–The time of day of the attack.

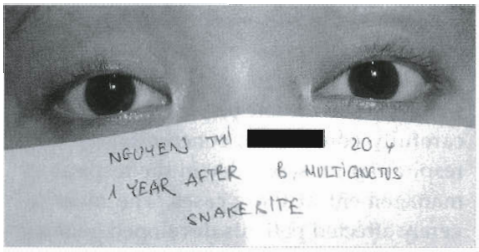

Fig 3–Persistent mydriasis one year after envenomation.

was also commonly noted. Among the laboratory results, the most surprising finding was a high rate of significant hyponatremia (serum sodium level less than 130 mmol/l) (Table 6). When it occurred, this occurred Day 2 or 3 after the snakebite.

The most commonly recorded complication was ventilator-associated pneumonia

Table 6
Extra-neuromuscular symptoms and signs commonly recorded during the ICU stay (N=60).

Symptoms and signs	*n* (%)
Tachycardia	50 (83)
Hypertension	26 (43)
Conjunctivitis	41 (68)
Corneitis	1 (2)
Hyponatremia	25 (42)

Table 7
The ICU management of the 60 envenomed patients.

Treatment given	*n* (%)
Endotracheal intubation	52 (87)
Tracheotomy	2 (3)
Mechanical ventilation	52 (87)
Antibiotic therapy	40 (67)
Sodium replacement	40 (67)
Ophthalmologic therapy (vitamin A, antibiotics)	48 (80)

due to long-term mechanical ventilation; this was observed in 37 patients (62%). Other important complications documented were infection of the urinary tract (23 cases) and ileus (2 cases). No antivenom was available during the study period. Supportive care, especially mechanical ventilation, was therefore the main treatment given. Fifty-two of the patients in the study population had to be endotracheally intubated for this purpose. The duration of artificial ventilation averaged 8.2 ± 7.3 days, ranging from 1 to 29 days. A majority of the patients were also treated with antibiotics and sodium replacement as well as local ophthalmologic therapy (Table 7).

The mean duration of the ICU stay in the study population was 12 ± 9 days, rang-

ing from 1 to 36 days. The hospital mortality rate was 7%; all 4 patients died in the ICU. Two died on admission to the ICU, another because of a malfunction of a ventilator, and the fourth died due to severe hyponatremia-induced brain damage. In addition, two patients suffered long-term sequelae. One had an anoxic brain injury and another became dependent on a tracheostomy cannula.

DISCUSSION

This study involves the largest number of patients severely envenomed by *B. multicinctus* reported in the literature so far. A few case series and epidemiologic studies have previously been reported, from the Southeast Asian region (Chan *et al*, 1995; Pe *et al*, 1997), Taiwan (Hung, 2004), and the south of China (Sawai *et al*, 1992). The major findings in this study were the high proportion needing mechanical ventilation and the high rate of acute hyponatremia. The study population was highly selective as all patients were admitted to an ICU. The 54 severe cases from the area surrounding Hanoi during the 4-year period show the grave prognosis if untreated.

In accordance with other case series, the bite by *B. multicinctus* was found to occur commonly in rural areas, where the habitats of snakes overlap those of humans (Chan *et al*, 1995; Hung, 2004). Agricultural workers clearly predominated among the victims. As with other krait species, such as *B. caeruleus* and *B. candidus* (Warrel *et al*, 1983; Kularatne, 2002), the attacks of *B. multicinctus* usually occur at night (Chan *et al*, 1995; Pe *et al*, 1997). The most common locations of the attacks in our study, the patients' homes and the rice field, are similar to those reported in other case series (Pe *et al*, 1997; Hung, 2004).

In previously reported *B. multicinctus* envenoming, the first neurological symptoms developed within a few hours after the bite (Chan *et al*, 1995; Pe *et al*, 1997), and in envenoming by other krait species, they appeared within 12 hours (Warrel *et al*, 1983; Seneviratne, 2002). In the present study the first symptoms developed within a wide time-range of 0.5 to 24 hours. This should be considered regarding the duration of observation required in these patients.

The neuromuscular symptoms and signs recorded in this study were in conformity with those described in previous case series of envenoming by *B. multicinctus* (Chan *et al*, 1995; Pe *et al*, 1997), as well as by some other kraits (Kanchanapongkul, 2002; Kularatne, 2002; Seneviratne and Dissanayake, 2002). Ptosis and ophthalmoplegia were frequently observed and often led to dry eyes and conjunctivitis, or even corneitis in one case. These events are important to recognize and require particular nursing care. Mydriasis was also recorded in the majority of patients. The dilatation of the pupils was often maximal and was extremely persistent in some cases (Fig 3). The commonly documented palatal paralysis with inability to swallow was one of the reasons for respiratory failure in the early phase of the ICU course, but was also a cause of extubation failure in some cases in the late phase. This should be carefully considered, concomitantly with respiratory muscle palsy in the respiratory management of these cases. The most severely affected patients developed generalized muscle paralysis and became completely unresponsive. This situation, combined with apnea and dilated pupils, may easily be misdiagnosed as brain death. Electroencephalography and nerve conduction studies therefore may be indicated in situations of uncertainty.

The envenomed patients in the study often experienced general myalgia (Table 5). Some patients still had pain and numbness several months after discharge, requiring analgesic therapy. This phenomenon re-

sembles the case of peripheral sensory neuropathy after a krait bite reported from Sri Lanka (Seneviratne and Dissanayake, 2002).

Tachycardia and hypertension were noted in many patients. These findings have been reported previously after snakebite by *B. multicinctus* (Chan *et al*, 1995) and also by another krait species, namely *B. candidus*. It has been suggested that these clinical features may be due to a decreased parasympathetic tone and may be treated with beta adrenergic blockers (Laothong and Sitprija, 2001).

The important finding of a rapidly developing significant hyponatremia in nearly half of the present study population was surprising. This electrolyte disturbance has not been reported previously after envenoming by *B. multicinctus*. We do not know the exact mechanism of the disturbance, but the sodium content of the urine was found to be elevated in a majority of the cases. Hyponatremia has been reported following bites by the American coral snake. The mechanism underlying the electrolyte disturbance after that snakebite was reported to be a natriuretic peptide in the venom (Ho *et al*, 1997). We strongly recommend that serum electrolyte levels be followed up in every patient envenomed by *B. multicinctus*, and that sodium be replaced immediately if necessary.

Fifty-two patients or 87% of the study population needed mechanical ventilation. This finding emphasizes the seriousness of snakebite from this particular species. The duration of the artificial ventilation in our study was longer than that in a study from India describing severe neuroparalytic pulmonary status after different snake envenomations (Aggarwal *et al*, 2001). The recorded hospital mortality rate of 7% in our study, despite ICU treatment, also underlines the danger of envenoming by *B. multicinctus*.

In conclusion, this study provides important information on envenoming by *B. multicinctus*. The new finding of a high rate of significant hyponatremia makes screening and prompt sodium replacement imperative, and the severe clinical features recorded indicate an urgent need for a specific antivenom.

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ORIGINAL STUDY

A Controlled Clinical Trial of A Novel Antivenom in Patients Envenomed by *Bungarus multicinctus*

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Abstract In northern Vietnam, a majority of severely envenomed patients are bitten by *Bungarus multicinctus*. Hitherto, these victims have received supportive care only. The aims of this study were to assess the possible efficacy and side effects of a new antivenom. This trial (ClinicalTrials.gov Identifier: NCT00811239) was performed during 2004–2006 at an ICU in Hanoi. For ethical reasons, the study was not randomized. All patients who fulfilled the inclusion criteria during 2004–2005 were prospectively enrolled, carefully recorded, and treated with optimal supportive therapy (control group). The patients who entered the study 2006 were treated with antivenom in addition to supportive care (antivenom group). The inclusion criteria were: envenomation by *B. multicinctus*, presence of systemic envenomation, and (during 2006) provision of written informed consent. Predefined endpoints were number of patients requiring mechanical ventilation, duration of mechanical ventilation, length of ICU stay, duration of muscle paralysis, and number of patients with ventilator-associated pneumonia. Eighty-one patients were included, 54 during 2004–2005 and 27 during 2006. Baseline characteristics were similar in the groups. The antivenom-group patients had a shorter duration of muscle paralysis of the limbs ($p<0.001$), of the diaphragm ($p<0.001$), and of ptosis ($p<0.001$). The duration of mechanical ventilation and length of ICU stay were shorter in the antivenom group ($p<0.001$). The rate of ventilator-associated pneumonia was lower in the antivenom group ($p<0.02$). However, the relative number of patients requiring mechanical ventilation was not reduced in the antivenom group. The rate of adverse reactions to the antivenom was 7.4%. A favorable efficacy and acceptable safety of this antivenom were demonstrated.

Keywords Antivenom · Snakebite · *Bungarus multicinctus* · Vietnam

Introduction

Venomous snakebites constitute a serious health problem in many Asian countries. It has been estimated that approximately 25,000–35,000 people die each year from snakebite in that part of the world [1]. In Vietnam, the burden of snakebites on public health motivated Calmette to conduct original studies at the Vaccine Institute in Saigon over a hundred years ago and to develop the first snake antivenom ever [2].

In northern Vietnam, a vast majority of the most severely envenomed patients are bitten by *Bungarus multicinctus* (many-banded krait, Chinese krait), which is the only krait species giving rise to significant morbidity and mortality in the area. Its venom contains toxins which can cause severe neuromuscular blockade, but which do not give rise to swelling or necrosis at the site of the bite [1]. Alpha-bungarotoxin is a postsynaptically active toxin which binds to the acetylcholine receptors preventing binding of acetylcholine. The result is a non-depolarizing type of neuromuscular blockade. Moreover, the venom also contains β and γ-bungarotoxins which act presynaptically and depress the release of acetylcholine from the nerve endings.

Previous presentation: no data of this manuscript has previously been presented.

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The presence of the latter toxins explains why attempts at treatment with cholinesterase inhibitors, such as neostigmine, have not been very effective [3, 4].

Supportive care is an important part of the management of snakebites, but antivenom administration is the mainstay therapy in the majority of medically significant cases of envenoming. Such specific therapy may dramatically reduce the consequences of the envenomation [5–7]. Although antivenoms against *B. multicinctus* are available in China and Taiwan, clinical reports regarding their efficacy have only rarely been published [3, 8, 9]. In some series of cases, antivenom treatment has been tried after snakebites by other *Bungarus* species, but with rather conflicting clinical results [10, 11]. In Vietnam, no specific antivenom against *B. multicinctus* has been available until recently, when it was developed and produced for clinical use. The aims of this study were to assess the effectiveness of this newly produced antivenom and to investigate its possible side effects.

Materials and Methods

This prospective controlled clinical trial was carried out during a 3-year period (2004–2006) at the Toxicological Intensive Care Unit (ICU) of Bach Mai Hospital in Hanoi. For ethical reasons and because the antivenom was not clinically available until 2006, the study was not randomized or blinded. All patients who fulfilled the inclusion criteria during the first two years of the study were prospectively enrolled, carefully monitored, and treated with optimal supportive therapy in the ICU (control group). The patients who entered the study during the third year were treated with antivenom therapy in addition to supportive care (antivenom group). The patients were enrolled on the basis of the following criteria: (1) envenomation by *B. multicinctus*, (2) presence of clinical signs of systemic envenomation (neuromuscular signs), and (3) (during the year 2006) provision of written informed consent (by close relative if the patient was unable to do so). Clinical data including a number of defined clinical and laboratory examinations were recorded for each case in a predetermined standardized protocol during the entire 3-year study period. The severity of the symptoms on recruitment was defined on the basis of the five-graded (0–4) Poisoning Severity Score (PSS) [12].

During the year 2006, the patients were informed about the possible benefits and risks of the antivenom treatment and were able to withdraw at any time during the trial for any reason. Five to ten ampoules of antivenom, depending on the severity of muscle paralysis, were diluted with isotonic glucose solution to a total of 50 ml and then infused intravenously by electric pump for a period of 1 h. The patients were monitored continuously during and after the infusion to assess the efficacy of the treatment and any adverse reactions. Six to 8 h after the end of the infusion, a second infusion was administered, under similar conditions, if no clinical improvement or adverse reaction had been noted. Clinical examinations, in accordance with the study protocol, were performed at least twice daily up to discharge. The patients were also followed up 1 month later and readmitted if associated symptoms developed or became worse.

Predefined outcome endpoints were number of patients requiring mechanical ventilation, duration of mechanical ventilation, length of stay in the ICU, duration of a defined degree of muscle paralysis, and number of patients who developed a ventilator-associated pneumonia. The study was conducted in accordance with the WHO Good Clinical Practice guidelines and the Declaration of Helsinki. The study design and the form for the written consent were approved by the Ethics Committee of Hanoi Medical University. Statistical analyses were performed using an independent-samples t test or the Mann–Whitney test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables. Differences were considered significant if the p value was <0.05.

Antivenom

Venom pools from more than 100 specimens of *Bungarus candidus* and *B. multicinctus* of different sizes, ages, and sexes were collected from Vietnam. After milking, venoms were immediately lyophilized and then detoxified with glutaraldehyde, filtered, and stored at 4°C in bottles. Immunization of horses with increasing doses of the antigen described above was performed once a month for 7 months. The immunoglobulin fraction from each of the pooled horse plasma samples was pepsin-digested and then salt-precipitated to produce $F(ab')_2$ fragments. The antivenom was supplied in liquid form, 2,000 units per ampoule. The antivenom was approved for the use under discussion in the manuscript by the National Institute for Control of Medico Biological Products, Ministry of Health in Vietnam, but it has not yet become a commercial product.

Results

During the 3-year study period, a total of 81 patients fulfilled the inclusion criteria and entered the study. Of these, 54 patients were included during the years 2004 and 2005 (control group) and 27 during 2006 (antivenom group). The baseline characteristics were similar in the two groups, and are presented in Table 1. Most patients were male and of a productive age. Children below the age of 15 years

Table 1 Baseline characteristics in the two study groups

Variables	Control group	Antivenom group	Significance
Age (years)	34±15	36±17	NS
Sex			NS
Male	38 (70%)	18 (67%)	
Female	16 (30%)	9 (33%)	
Time to development of first symptom (hours)	3.1±2.7	2.7±1.9	NS
Duration from snakebite to admission (number of patients)			NS
Within 6 h	13 (24%)	9 (33%)	
>6 h	41 (76%)	18 (67%)	
Site of bite			NS
Limb	49 (91%)	25 (93%)	
Trunk	3 (6%)	1 (4%)	
Unknown	2 (4%)	1 (4%)	
Severity score on recruitment			NS
Moderate (PSS 2)	9 (17%)	4 (15%)	
Severe (PSS 3)	45 (83%)	23 (85%)	

NS not significant; *PSS* poisoning severity score [12]

represented 14% of the study population and elderly patients (>60 years) accounted for 4%. Most of the patients developed their first symptoms within approximately 3 h after the snakebite, and were admitted to the ICU later than 6 h after the bite. All included patients displayed moderate or severe envenomation on admission according to the PSS criteria, with similar severity in the two groups.

The time span between the snakebite and the start of antivenom therapy was 19±9 h, ranging from 5 to 38 h. Twenty patients were treated by antivenom within 24 h after the bite (only two patients within 6 h). The average dose of administered antivenom was 8.1±3.2 ampoules, ranging from 5 to 17 ampoules.

The patients in the antivenom group had a significantly shorter duration of paralysis of the extremities, the diaphragm, and of ptosis. Hyponatremia was a common finding in the study population. The proportion of patients with marked hyponatremia (serum sodium level of less than 130 mmol/L) was somewhat lower in the antivenom group, and severe hyponatremia (sodium level <120 mmol/L or symptomatic) was only observed in the control group (two patients). The rate of ventilator-associated pneumonia was significantly lower in the antivenom group (Table 2).

Table 3 presents the treatment measures in the two groups. There was no fatality. The relative numbers of patients requiring endotracheal intubation and mechanical ventilation were similar in the two groups. However, the duration of mechanical ventilation and endotracheal intubation and the length of the ICU stay were significantly shorter in the antivenom group. No treatment with any cholinesterase inhibitor was given during the 3-year study period.

In the seven patients treated with antivenom later than 24 h after the snakebite, the duration of mechanical ventilation and the length of the ICU stay were longer than those in the 20 patients who received antivenom within 24 h (Mann–Whitney test, p values 0.07 and 0.01, respectively).

No patient in the study developed severe acute anaphylaxis. The rate of adverse reactions was 7.4% (2/27). A moderate allergic reaction in the form of urticaria was noted in one patient. Liver transaminase levels were transiently increased in another patient, in whom the maximum values of aspartate transaminase (AST) and alanine transaminase (ALT) were observed on the fifth day (344 and 442 U/L, respectively, or approximately ten times the upper reference levels). Serum sickness was not observed in the study.

Table 2 A comparison between the two groups regarding some clinical findings during the stay in the intensive care unit

Clinical findings	Control group	Antivenom group	Significance (p)
Duration of limb paralysis (days)	7.5±6.9	2.2±2.6	<0.001
Duration of diaphragm palsy (days)	7.0±7.0	1.6±1.6	<0.001
Duration of ptosis (days)	6.3±4.7	3.5±1.5	<0.001
Hyponatremia with serum Na <130 mmol/L (number of patients)	27 (50%)	9 (33%)	0.16
Ventilator-associated pneumonia (number of patients)	27 (50%)	6 (22%)	0.02

Table 3 A comparison between the two groups regarding some treatment measures during the intensive care unit (ICU) stay

Outcome measures	Control group	Antivenom group	Significance (p)
Duration of mechanical ventilation (days)			<0.001
Mean (±SD)	8.6±8.1	2.3±2.5	
Range	0–31	0–12	
Duration of intubation (days)			<0.001
Mean (±SD)	10.1±9.3	3.0±2.6	
Range	0–40	0–12	
Length of ICU stay (days)			<0.001
Mean (±SD)	11.6±9.7	6.1±3.2	
Range	1–46	1–15	
Number of patients requiring mechanical ventilation	44 (81.5%)	23 (85.2%)	NS

NS not significant

Among the patients in the control group, none developed any allergic reaction and none had significantly but transiently elevated liver enzymes.

Discussion

The major findings in this clinical trial were the favorable clinical efficacy of the tested antivenom and the lack of severe adverse reactions to this treatment. The significant results of the study were achieved despite the fact that 93% of the patients in the interventional group received the antivenom therapy more than 6 h after the snakebite.

Although an improvement of most tested symptoms was demonstrated in the antivenom group in the present study, the relative number of patients requiring mechanical ventilation was not reduced. The considerable delay before ICU admission is the likely explanation. The reason why some patients had to stay endotracheally intubated also after they had been weaned from the ventilator (Table 3) was that a palatal paralysis with inability to swallow sometimes persisted longer than the paralysis of the respiratory muscles.

A high rate of hyponatremia was observed in the study population as was also reported in a previous study on snakebite by this particular species [13].

The average dose of the antivenom used in the present study was similar to the dose regimen used in a study in China, and in accordance with the recommended doses of other antivenom products used against bites by this *Bungarus* species [9]. With the aim of protecting its stability, the antivenom was not diluted in large amounts of solution in our study, but nevertheless was infused slowly during a period of 1 h. Since skin testing is today not only considered unnecessary but also misleading, and pretreatment with antihistamine, epinephrine, or corticosteroids is controversial, neither a skin test nor any pretreatment was performed in the present study [14–17].

The reported frequencies of adverse reactions after different types of antivenom therapies have varied considerably. Acute reactions in 23–56% of the patients and high frequencies of serum sickness (up to 75%) have been recorded, but in other studies the rates of these complications have been rather low or approximately 10% [5, 18–20]. The main explanation for this discrepancy is that the older immunoglobulin-based antivenoms had several side effects, whereas more recent, purer equine antivenoms, containing $F(ab')_2$ or Fab fragments, produce few side reactions [21]. In our study, no severe reactions were recorded and a single moderate reaction was observed in a patient who developed urticaria. This was probably due to the high quality of the $F(ab')_2$ antivenom in combination with rational dosing and slow administration. The transiently increased level of transaminases observed in another patient may possibly have had another, unknown explanation.

In view of the method of production of this new antivenom, it seems reasonable to assume that it should also be effective after bites by *B. candidus* (Malayan krait). However, this remains to be shown in a clinical trial.

Limitations of the Study

Unfortunately, it was not possible to perform this study as a randomized placebo-controlled trial. Therefore, we cannot exclude that a certain degree of unintentional bias may have influenced the recordings in the study protocol, even though every effort to avoid this was undertaken.

Conclusion

In conclusion, the efficacy and safety of this new antivenom were clearly demonstrated in this controlled clinical trial of patients bitten by *B. multicinctus*.

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IV

POTENTIALLY HAZARDOUS ENVIRONMENTAL FACTORS FOR POISONING IN RURAL VIETNAM: A COMMUNITY-BASED SURVEY

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Abstract. Poisoning represents one of the most common threats against public health. This population-based study was undertaken to identify potentially hazardous environmental factors for poisoning in Vietnam, and thereby to improve the background information needed to take adequate preventive measures. The study population comprised 3,814 individuals from 942 randomly selected households in Phu Tho Province. Their mean age was 32.7 years, 50.4% were male. Data collection methods included face-to-face interviews using a structured questionnaire, and reality observations following a structured checklist. Of the study population, 438 individuals (11.5%) recalled having suffered from at least one episode of symptomatic poisoning. The toxic agents most commonly involved in these incidents were pesticides (68.7%). Hazardous exposure to toxins was reported to occur frequently and pesticides were again the agents most commonly involved. The presence of insecticides and other pesticides in the home were common (39%) and 21.7% of studied households kept poisonous chemicals in places easily accessible to children. Nearly half the households kept medications at home, often without any medical safe-box. Fifty-six point two percent reported prescriptions were not necessary for purchasing pharmaceuticals. Common habits among household members put them at risk for poisoning by natural toxins. Among these, frequent use of unusual herbs, and the practice of raising and eating poisonous animals were most important. In conclusion, the widespread use of pesticides, risk for exposure to natural toxins and self medication constitute major hazards for poisoning in Vietnam. Effective control regulations and safe strategies are lacking.

Key words: poisoning, environmental factor, pesticide, toxin, Vietnam

INTRODUCTION

Poisoning is one of the most common threats to public health worldwide (Peden *et al*, 2002). Defined as drug overdose, food poisoning, or symptomatic exposure to an environmental toxin, poisoning is a pervasive health care problem. The panorama of frequently occurring toxins and exposure hazards differs considerably from country to country. Thus, epidemiological studies with toxicological surveillance data for each country are necessary to determine countries' specific problems and risks, so that preventive measures can be taken. However, toxico-epidemiological data from developing countries are sparse

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(Peden *et al*, 2002). Moreover, most published studies on acute poisoning are hospital-based (Liu *et al*, 1997; Fathelrahman *et al*, 2005; van der Hoek and Konradsen, 2006) and the reports are often based on data from highly selected patient populations. Examples of published surveys of poisoning in rural areas of different developing countries are from Brazil (Presgrave *et al*, 2008), Malaysia (Fathelrahman *et al*, 2005) and Thailand (Wanankul *et al*, 2007).

Vietnam is a low-income, agricultural country in which toxic exposure is common, and poisoning has had an important impact on public health. Vietnam has an area of nearly 330,990 km^2 and a population of approximately 85 million. We recently reported characteristics of and clinical findings in patients with acute poisoning admitted to the first toxicological intensive care unit in northern Vietnam (Hung *et al*, 2008). The aim of the present study was to identify the most commonly occurring exposure hazards and other risks of acute poisoning in rural areas of northern Vietnam, and to improve the background information needed to take adequate preventive measures.

MATERIALS AND METHODS

This cross-sectional population-based epidemiological study was conducted in Phu Tho Province, northern Vietnam during the year 2008. This province is situated at the apex of the Red River delta linking Hanoi with the northern mountainous provinces (Fig 1). Its area is 3,519 km^2, corresponding to 1% of the whole country, and its population in the year 2006 was about 1.3 million, approximately 1.5% of the total country population. The rural population of Phu Tho accounts for 85% of its total inhabitants, a proportion which resembles that of all of Vietnam. There are

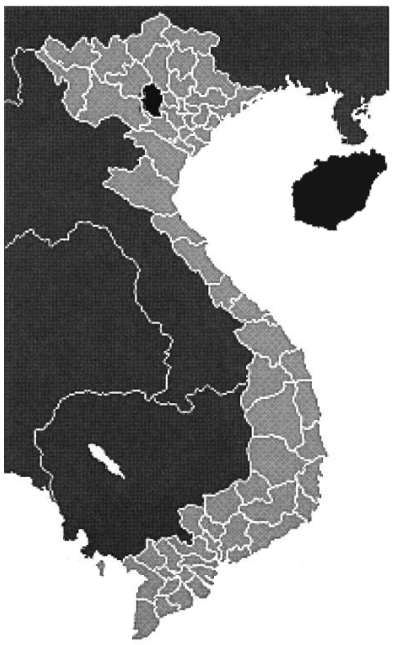

Fig 1–Map of Vietnam and Phu Tho Province.

13 local administrative regions (11 districts, one city, and one township) in Phu Tho Province, comprising a total of 273 communes. Among these, 2 out of 12 communes in Lam Thao District were chosen as the study setting. The inhabitants of these two communes are representative of Vietnam regarding occupational distribution and the communes are typical of Vietnam regarding population density and nature of agriculture. The main crops in the study area are rice and different kinds of vegetables, similar to most of rural Vietnam.

The study population initially comprised 1,000 randomly selected households in the two above mentioned communes, which consisted of 23 villages. After giving informed consent, 942 households comprising 3,814 individuals, were finally enrolled in the study. The data col-

lection methods included face-to-face interviews using a structured questionnaire, and reality observations following a structured checklist. The questionnaire covered information about demographic features and general epidemiological points, poisoning events, and risk factors for poisoning. Poisoning was defined as drug overdose, food poisoning, or any symptomatic exposure to an environmental toxic substance. The checklist included the presence of pesticides, other toxic chemicals, pharmaceuticals, or drugs of abuse at home, and safe storage methods, equipment for preparation and use of pesticides, and existence of poisonous plants or animals. Pesticides commonly used in Vietnam include insecticides (mostly organophosphorus compounds and carbamates), herbicides, and rodenticides (several toxic agents).

RESULTS

Of the total study population of 3,814 persons, 1,921 (50.4%) were male. Their mean age was 32.7 ± 19.7 (range 1 - 94) years. The study population consisted of 942 families (households). The mean number of family members was 4.0 ± 1.2 (range 1-8) people. A majority of the study population were agricultural workers. Other common occupations were students, industrial laborers and commercial workers (Table 1).

Hazardous exposure to toxic agents commonly occurred. Pesticides and other chemicals used in agriculture were the most frequently involved toxic compounds (Table 2).

Of the total study population, 438 individuals (11.5%) recalled having suffered from at least one symptomatic episode of acute poisoning. The toxic agents reported to be most commonly involved in these incidents were different kinds of pesticides (Table 3).

Table 1
Occupational distribution of the study population.

Occupation	*n* (%)
Agricultural worker	1,981 (51.9)
Student	917 (24.0)
Industrial worker	332 (8.7)
None	254 (6.7)
Commercial worker	97 (2.5)
Small child	48 (1.3)
Housewife/husband	7 (0.2)
Other or unknown	178 (4.7)
Total	3,814 (100)

Table 2
Occurrence of hazardous exposure to toxic agents.

Toxic agent	Household, *n* (%)
Insecticides	783 (83.1)
Herbicides	601 (63.8)
Household products	223 (23.7)
Rodenticides	202 (21.4)
Adulterant chemicals	23 (2.4)
Industrial chemicals	22 (2.3)
Preservation chemicals	19 (2.0)
Toxic gases	1 (0.1)

Among the studied households, 48 (5.1%) reported having at least one family member with some chronic medical consequence of a poisoning. None of these sequelae was life-threatening, but were graded as mild to moderate. Examples of these chronic symptoms included general tiredness, weakness and numbness of distal extremities. They were most commonly (71%) the consequence of exposure to pesticides.

Table 3
Toxic agents reported to have been involved in the most recently occurring symptomatic poisoning episode among the study population.

Toxic agent	*n* (%)
Pesticides	301 (68.7)
Pollution	8 (1.8)
Other chemicals used in agriculture	5 (1.1)
Food poisoning	4 (0.9)
Industrial chemicals	2 (0.5)
Medications	1 (0.2)
Other or unrecognized	117 (26.7)

Table 4
Toxic agents kept at home.

Toxic agent	Presence in household, *n* (%)
Insecticides	294 (31.2)
Chemical household products	274 (29.1)
Herbicides	44 (4.7)
Rodenticides	21 (2.2)
Adulterant chemicals	6 (0.6)
Industrial chemicals	4 (0.4)
Preservation chemicals	3 (0.3)
Other toxic chemicals	119 (12.6)

Table 5
Sources of information concerning methods of safely keeping toxic agents at home.

Source of information	Households, *n* (%)
Seller	479 (50.8)
Agricultural expert	303 (30.2)
Self-learning from other sources	293 (31.1)
Media	275 (29.2)
Relatives, friends, neighbors	97 (10.3)
None	66 (7.0)

Concerning the presence of toxic agents in the home, different pesticides were again the most common. Other common toxic agents kept at home were household chemical products and agrochemicals (Table 4).

A majority of households had obtained knowledge regarding safely storing toxins directly from sellers. Only one-third of households had received the necessary knowledge to correctly store chemicals from an appropriate person such as an agricultural expert. Approximately 7% of households had not been given any information concerning safely storing chemicals (Table 5).

Among the studied households, 204 (21.7%) reported that they had kept poisonous chemicals in places accessible to children, and 505 (53.6%) had never locked chemical storage boxes or drawers. One hundred thirty-one households (13.9%) had not kept hazardous chemicals in their original containers, and among these, 33 (3.5%) had used food containers to keep poisonous chemicals. More than a fourth of the households (27.7%) did not have a habit of explaining to their children about the risks of toxic chemicals.

The risk of overdosage of pharmaceuticals was also seen in this study. Nearly half the households kept medications at home, but only one-fourth had any medical safe-box. A large proportion of households (56.2%) reported prescriptions were not necessary for purchasing pharmaceuticals.

Some common habits of the studied households put their members in danger of poisoning by natural toxins. Among these, frequent use of herbs, and raising and eating poisonous animals, were the most important hazardous practices (Table 6).

Table 6
Possible risk factors for natural toxin poisoning.

Possible risk	Households, *n* (%)
Collection and ingestion of unusual herbs[a]	292 (30.1)
Use of poisonous animals as food	241 (25.6)
Honey collection from bee and wasp nests	125 (13.3)
Raising poisonous animals	86 (9.1)
Ingestion of animal gallbladders	30 (3.2)

[a]After advice from quacks in approximately half the households.

When observing the problem with their own eyes, the interviewers found pesticides were present in 369 of the households (39%). Pesticides were most commonly kept in containers without a lock (97.5%). The presence of pharmaceuticals at home was found in 564 households (60%). Besides bees' nests, which were common, venomous snakes were seen to be raised in 75 of the households and poisonous toads in 14.

DISCUSSION

The major finding in this study was that the availability and accessibility of pesticides constitute the main risk factor for poisoning among ordinary people in Vietnam. This is partly explained by the fact that many kinds of highly toxic insecticides, herbicides, and rodenticides are widely available and commonly used in Vietnam, and partly by the lack of effective regulations and strategies to reduce this threat to public health. Acute poisoning by agricultural pesticides is a well established public health problem in developing countries, with an estimated 300,000 deaths annually worldwide (Gunnell and Eddleston, 2003). Previous scientific reports have suggested that the widespread availability of pesticides in rural communities is a crucial risk factor in the majority of fatal self-poisonings (Eddleston and Phillips, 2004; Konradsen *et al*, 2006). Easy accessibility of pesticides to adults and children is also a reality in many developing countries, such as Sri Lanka and China (Liu *et al*, 1997; Hawton *et al*, 2009). This fact requires a prompt poison-prevention approach to reduce the availability of pesticides, especially those that are most toxic.

A second finding in this study was that another important source of toxins in rural areas of Vietnam is its poisonous flora and fauna. The hazardous habit of ingesting and otherwise using unusual and unknown herbs reflects the fact that remedies and traditional medicines are popular in this area, and many Vietnamese people do not believe herbs are toxic. The lack of necessary public information and control regulations makes the situation worse. This is an important problem not only in many Asian countries but also in other parts of the world (Liu *et al*, 1997; Deng, 2002). The belief that ingestion of poisonous animals is good for health has resulted in the fact that many households raise venomous snakes for economic reasons, and life-threatening envenomations are not uncommon in Vietnam (Hung *et al*, 2009).

Another risk factor for poisoning found in this study was the availability and inadequate storage of hazardous household products. Such products were commonly within reach of children and were sometimes stored in beverage bottles, thereby constituting a risk for unintentional poisoning. This finding is consistent with previous reports from other regions (Sawalha, 2007; Wananukul *et al*, 2007; Presgrave *et al*, 2008).

Self-medication, through retail pharmacies without professional consultation, was commonly found in this study. The problem of drug utilization and self-medication in Vietnam has been reported previously (Okumura *et al*, 2002). In a recently published hospital-based study on poisoning in Vietnam (Hung *et al*, 2008), pharmaceutical overdose was recorded as one of the most common types of acute poisoning.

The limited sample size and cross-sectional design of this epidemiological study make it impossible to draw any conclusions from the results regarding the incidence of severe poisoning in Vietnam. Moreover, the question in the interview questionnaire concerning previously occurring poisoning episodes was not possible to be validated, and therefore constitutes another limitation of the study. However, to our knowledge, this is the first population-based study in English regarding hazardous environmental factors for poisoning in Vietnam.

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