2018 Joint Conference of Poison Control Centres

# New Developments in Prevention *and* Management of Poisoning

## 27 JULY | PROGRAMME BOOK

**Lecture Theatre, Ground Floor**
**Centre for Health Protection**
**147C Argyle Street, Kowloon**

### Organisers

**Prince of Wales Hospital**
**Poison Treatment Centre**
Hospital Authority, Hong Kong

**Centre for Food and Drug Safety**
Faculty of Medicine
The Chinese University of Hong Kong
Hong Kong

## Opening message from the Deputy Director of Health

I wish to congratulate the Prince of Wales Hospital Poison Treatment Centre of Hospital Authority and Centre for Food and Drug Safety of the Chinese University of Hong Kong on their admirable efforts in organising the 2018 Joint Conference of Poison Control Centres. I would also like to take this opportunity to congratulate the Drug and Poisons Information Bureau of the Chinese University of Hong Kong on its 30th Anniversary.

Like many other jurisdictions, poisoning is an important public health issue in Hong Kong. The Hong Kong SAR Government is committed to strengthening the capacities and facilities in the prevention and control of poisoning and is also fully aware of the importance of multi-disciplinary approach in poison control. Established in April 2007 with a view to enhancing and coordinating poison prevention and management efforts across sectors and clinical specialties, the Hong Kong Poison Control Network consists of four key components, namely the Hong Kong Poison Information Centre at United Christian Hospital, the Poison Treatment Centre at Prince of Wales Hospital, the Toxicology Reference Laboratory at Princess Margaret Hospital, and the Toxicovigilance Section of the Department of Health. Over the last decade, we have witnessed and are pleased to see that joint efforts and close collaboration between clinical services and the public health system have brought significant progress in the control of poisoning in Hong Kong.

The conference provides a platform for overseas and local speakers to address a broad range of topics on prevention and control of poisoning, including topics from a broad national or regional perspective to specialised issues on clinical management of poisoned patients. I wish the conference every success, our overseas guests a lovely stay in Hong Kong, and everyone a pleasant and rewarding experience.

Dr. Amy P.Y. Chiu, JP
Deputy Director of Health, The Government of the Hong Kong SAR
Chairperson of Hong Kong Poison Control Network

## Welcome message from the Chairman of the Organising Committee

Poisoning remains an important public health problem worldwide, and the Asia Pacific region, especially its rural areas, carries a disproportionately heavy share of the burden. Poison control centres and their multidisciplinary teams are working hard at full capacity to prevent poisoning, improve the care of the poisoned patients and handle new challenges. Also because of the ever increasing demand for expertise in complex cases and emerging poisons, strategic collaboration among clinical toxicology centres and leadership in prioritising the action plans are of obvious importance. The need for close collaboration in the region has long been recognised. Following the fruitful discussion in previous APAMT meetings and our joint conferences in Hong Kong, it is decided that the Asia Pacific Network and Clinical Toxicology Centres (APNCTC) should be established to serve these purposes.

In Hong Kong, more structured clinical toxicology services can be dated back to 30 years ago, when the Drug and Poisons Information Bureau was set up. With the generous support of the Government of the Hong Kong SAR, major enhancements occur since 2005, when designated centres to provide tertiary level poisons information, poison treatment, toxicology laboratory, and toxicovigilance services. Hong Kong Poison Control Network (https://www.hkpcn.org.hk) was launched in 2007 to enhance and coordinate the poison prevention and control efforts.

As in previous years, Prince of Wales Hospital Poison Treatment Centre and Centre for Food and Drug Safety, Faculty of Medicine, the Chinese University of Hong Kong are honoured to host this Joint Conference, with support from poison control centres and clinical toxicologists in the region and Past Presidents and Honorary Fellows of Asia Pacific Association of Medical Toxicology. The 2018 Conference Theme "New Developments in Prevention and Management of Poisoning" serves to emphasise the continuing needs for exchange of expertise, team efforts, preparedness and regional collaboration in poison prevention and control. There are two special symposia to celebrate the establishment of APNCTC and the 30th Anniversary of DPIB.

I hope you all engage in making this Conference a stimulating forum for sharing experience and exchanging ideas. I wish all overseas speakers a pleasant stay in Hong Kong.

Prof. Thomas Y.K. Chan, BBS, JP
Chairman, Organising Committee
Director, Prince of Wales Hospital Poison Treatment Centre
Director, Centre for Food and Drug Safety
Faculty of Medicine, The Chinese University of Hong Kong

# Organisers and Organising Committee

## Organisers

Prince of Wales Hospital Poison Treatment Centre
Hospital Authority, Hong Kong

Centre for Food and Drug Safety
Faculty of Medicine
The Chinese University of Hong Kong, Hong Kong

## Participating Centres

Centre for Food and Drug Safety, CUHK, Hong Kong

Mashhad Medical Toxicology Centre (MMTC), Iran

National Poison Center, Taipei Veterans General Hospital, Taiwan

National Poison Control Center, China CDC

Prince of Wales Hospital Poison Treatment Centre, HA, Hong Kong

Ramathibodi Poison Center, Bangkok, Thailand

## Organising Committee

Prof. Thomas Y.K. Chan (Chairman)

Prof. Reza Afshari
Prof. Juliana C.N. Chan
Dr. Jou-Fang Deng
Prof. Brian Tomlinson
Dr. Raymond S.M. Wong (Secretary)
Dr. Jones C.M. Chan
Dr. Elaine Y.K. Chow
Dr. Chengye Sun
Prof. Winai Wananukul

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## Programme

### *8:30 – 9:00 Registration*

**9:00 – 9:03 WELCOME REMARKS**

Prof. Thomas Y.K. Chan, BBS, JP
Chairman, Organising Committee, and
Director, Prince of Wales Hospital Poison Treatment Centre, and
Director, Centre for Food and Drug Safety

**9:03 – 9:08 OPENING ADDRESS**

Dr. Amy P.Y. Chiu, JP
Deputy Director of Health
The Government of the Hong Kong SAR, and
Chairperson of Hong Kong Poison Control Network

**9:08 – 9:15 GROUP PHOTOS**

**9:15 – 10:50 ASIA PACIFIC NETWORK OF CLINICAL TOXICOLOGY CENTRES SYMPOSIUM**

**Chair Persons:**

Dr. Jou-Fang Deng

Dr. Chengye Sun

Prof. Winai Wananukul

**9:15 – 9:20 Asia Pacific Network of Clinical Toxicology Centres**

Prof. Thomas Y.K. Chan

**9:20 – 9:50 Poison Control in Mainland China – Current Status and Future Developments**

Dr. Chengye Sun

**9:50 – 10:20 Poison Control in the Asia Pacific Region – Achievements and Successes**

Prof. Winai Wananukul

**10:20 – 10:50** **Poison Control in the Asia Pacific Region – Emerging Challenges**

Dr. Jou-Fang Deng

## *10:50 – 11:10 Tea Break*

## 11:10 – 12:30 Emergency Management and Assessment of the Poisoned Patients

**Chair Persons:**

Prof. Reza Afshari

Dr. Jones C.M. Chan

**11:10 – 11:30** **Assessment and Management of the Acutely Agitated and Violent Adults**

Dr. Man Li Tse

**11:30 – 11:50** **Cluster of Acute Poisonings Associated with a Ketamine Analogue, 2-oxo-PCE**

Dr. Tony W.L. Mak

**11:50 – 12:10** **Availability and Accessibility of Antidotes in Acute Hospitals**

Dr. Raymond S.M. Wong

**12:10 – 12:30** **Acute and Late Complications of Chemical Warfare Agents**

Prof. Reza Afshari

## *12:30 – 14:00 Lunch*

## 14:00 – 16:00 Drug and Poisons Information Bureau 30th Anniversary Symposium

**Chair Persons:**

Prof. Brian Tomlinson

Dr. Raymond S.M. Wong

**14:00 – 14:30** **Medicines Discovery, Development and Evaluation**

Prof. Juliana C.N. Chan

**14:30 – 15:00** **Therapeutic Drug Monitoring in Clinical Toxicology and Drug Safety**

Prof. Reza Afshari

**15:00 – 15:20** **Antidotes for Opioid Poisoning**

Dr. Jou-Fang Deng

**15:20 – 15:40** **Management of Venomous Snakebites**

Prof. Winai Wananukul

**15:40 – 16:00** **Prevention of Hypersensitivity Drug Reactions**

Dr. Jones C.M. Chan

## Asia Pacific Network of Clinical Toxicology Centres

*Prof. Thomas Y.K. Chan, The Chinese University of Hong Kong, Hong Kong*

Asia Pacific Network of Clinical Toxicology Centres is established to provide the platform for strategic collaboration and leadership in prioritising the action plans for poison prevention. The Network will be led by the Steering Committee, consisting of the directors, former directors or senior staff of clinical toxicology units in the region and world renowned experts. The emphasis will be on the primary prevention of poisoning, the vulnerable groups, environmental hazards, drugs or chemicals with a high fatality index, and neglected or emerging poisons. The Network will try to facilitate regional collaboration in clinical toxicology services, research and training. The recommendations from the Network will be disseminated at scientific conferences and via regular bulletins and medical journals.

There are numerous examples of hidden hazards that can pose a serious threat to public health. Very rarely, methanol can exist as an unlisted ingredient in supposedly alcohol based hand rub. Unintentional ingestion by children and inadvertent consumption by older subjects as alcohol (ethanol) substitute can occur. If repeatedly used as a hand rub, dermal absorption resulting in chronic toxicity occurs, especially if desquamation and dermatitis are present. Skin-lightening cosmetic products containing mercury can cause nephrotic syndrome. In view of the presence of mercury toxicity, elevated urine mercury levels and its aetiological importance, chelation therapy (e.g. DMPS or DMSA) should be given. Proteinuria improves together with decreases in urine mercury levels, and urinary protein excretion generally normalises long before urine mercury levels. The adjunctive role of corticosteroids is unclear. Aflatoxins are mycotoxins produced by two species of *Aspergillus*, which are found especially in regions with hot and humid climates. They are genotoxic and carcinogenic, and their levels in foods are regulated. However, reminders for the public to consume related food products within days after opening package are often absent in the product labels. This overlooked source of aflatoxin exposures increases the risk of liver cancers in subjects with chronic hepatitis B or C infections. Lead is neurotoxic, and the developing brain and young children are the most susceptible. Its adverse effects on IQ and the increased risk of neurobehavioural problems are well known. Blood lead levels in childhood are associated with lower adult IQ and socioeconomic status nearly three decades later. Therefore, exposures to lead in foods, the environment, air and drinking water must be kept as low as possible.

# Poison Control in Mainland China – Current Status and Future Developments

*Dr. Chengye Sun, National Poison Control Center, China CDC*

中國大陸毒物危害大體上分為兩個階段，從建國到 1978 年是第一階段，這個時期是以計劃經濟為主體，人和物的流動都是在計畫體系下流動，毒物中毒發生規律明晰，與之相配套的管理和服務體系完整，雖也出現過多起較大的群體性中毒事件，但總體上毒物危害被控制在較為平穩的狀態；1978 年底大陸啟動改革開放，實行市場經濟政策，人和物都有市場調配，生產和市場都十分活躍，人員流動性大，中毒發生人群、地點、種類均有較大變化。第一階段主要中毒發生在職業場所和居民家中，以金屬中毒、農藥中毒、細菌毒素中毒最為突出；在第二階段，金屬、農藥中毒明顯減少，有毒生物中毒發生頻次和危害增加明顯，藥物中毒普遍。化工產業的迅速發展，潛在洩漏風險增加，重大中毒事件也增加較快，如 2015 年天津濱海新區危化品庫爆炸事件造成 165 人死亡，數萬人受累。

大陸中毒控制工作是從上個世紀末起步，工作重點是毒物資訊服務、中毒患者救治、重大危害控制、突發事件應急等，有了一定進展，但與香港、臺灣，以及西方國家差距大，面對問題不同，國情差異大，未來發展也有有所不同。如資訊服務網路在發展電話服務的同時，利用廣泛普及的移動終端開展中毒資訊服務，把毒物監測與服務結合，利用資訊技術成果提升服務水準，強化突發事件應急能力建設，減少和控制危害程度；結合國家體制調整，完善毒物控制體系，使其更有效率，更好滿足公眾需求。系統研究毒物危害和中毒預防、診斷治療規律，促進醫學毒物學形成和發展也是未來幾年要進行的工作，在中國發展大背景下，促進相關法律完善，用法律保障公眾免受危害是一個長期的工作。

# Poison Control in the Asia Pacific Region – Achievements and Successes

*Prof. Winai Wananukul, Ramathibodi Poison Center, Bangkok, Thailand*

Poison control is generally a mission of most poison control centres. In the past, many of poison control centers in this region were initiated by International Programme of Chemical Safety (IPCS). Unfortunately, IPCS plays less role for the development and coordination of poison centres for many years**.** Therefore, most of them have individually developed and set their own missions. Now, many poison centres have succeeded and achieved their goals to such an extent. Thailand, for example, the service of poison centre is well recognized among healthcare in Thailand. In addition, the centre has been able to detect many toxicological outbreaks and bring to prevention measures. Lead poisoning form recycle factories and an outbreak of botulism during Thai New Year Holiday are the recent examples. Due to shortage of some antidotes, the centre collaborates with other related government agencies to initiate the "National Antidote Programme". Stockpiles of the orphan antidotes and antivenom as well as a new system to manage the drugs have been set up since 2010. The objective is to ensure that all people living in Thailand be able to gain access to the antidotes. During the operation, the project has proved its efficacy. The programme is able to supply necessary antidotes for some toxicological incidents in neighboring countries such as Myanmar and Laos. Recently, the programme has provided botulinum antitoxin for 2 patients in Nigeria after an international call for support from Nigeria.

An outbreak of slimming pill associated psychosis in Hong Kong in 2014 was an example of network cooperation between Thailand and Hong Kong. Since there is no official body of network for poison center to communicate, it is currently done on a personal basis. This meeting will be a good starting point for official collaboration among poison centers in Asia Pacific region. The strong and well developed centres would be the core for the network to support developing national poison centres in Asia Pacific region. The final goal is to make this region having a well poison control system and safe from all toxicological threats.

# Poison Control in the Asia Pacific Region – Emerging Challenges

*Dr. Jou-Fang Deng, National Poison Center, Taipei Veterans General Hospital, Taiwan*

The concept and practice of poison control has been adapted and implemented in Asia-Pacific region since late 20th century. In the past, agrochemical poisonings involved with pesticides and herbicides have been the main issue among most of the countries which economically relied on the agricultural industry. After so many years, intentional organophosphate poisoning is still an important challenge to the medical professionals though paraquat poisoning is expectedly to be less since it has been banned for use in most of the regional countries.

However, there is a tendency that we might face more new pesticides, e.g. Chlorfenapyr, with an action mechanism to interfere the mitochondria function upon exposures. Before more pharmacokinetic and pharmacodynamic data is available, we will be still in a dilemma while managing the poisonings, since there is a lack of the information about the toxic dosage, the volume of distribution and the time when they will reach the peak upon ingestion. Therefore, not even to predict the progressive development, the measures for intervention and the outcome of the exposure.

Snake bites envenoming is another important issue but has been ignored among most of the tropical and subtropical countries such as Indonesia, Malaysia, Vietnam, Sri Lanka, Bangladesh as well as India. Fortunately, the WHO general assembly has adapted it into global agenda on the day of 2018-05-24, and a lot of research on the action mechanism, diagnosis and treatment for snake bite envenoming will be expectedly coming up step by step.

Drug abuse poisoning, apparently will come to us without any notice, since the availability of internet supply has been so convenient. The NSP and narcotics (synthetic, semisynthetic and natural narcotics) poisonings are currently overwhelming in Europe and particularly in North America, which we believe that it will bring us a big challenge in the near future.

Industrial chemical splashes occurred frequently in the developing country while on the way to the industrialization due to a lack of safety and health practice occupationally in the daily operation of manufacturing industry. Any way which will help to minimize the injury directly related to chemical splashes needs to be brought in and implemented for front line decontamination on the operation site.

Herbs, plants, animal products as well as other alternative medicines has been utilized for health care as well as health promotion in many countries among the region, particularly in those countries with prominent historic cultures such as India and China. Some of the so called natural products which either is toxic itself or contaminated and perhaps adulterated with heavy metals continuously to be another challenge in our daily practice. Just like the practice of pharmaceutical medicine, a phenomena of drug-drug interaction may occur while using the herbal products, which, however, is not easily to be identified unless a capable analytic laboratory system can be built up and got into practice to illustrate the existing mystery.

## Assessment and Management of the Acutely Agitated and Violent Adults

*Dr. Man Li Tse, Hong Kong Poison Information Centre, United Christian Hospital, Hong Kong*

The management of acutely agitated and violent patients can be difficult and is considered a high risk procedure in the emergency medical setting. Many clinicians might not aware that severe agitation is a life-threatening medical emergency. It causes end-organ injuries in a complex state of hyperthermia, lactic acidosis, electrolyte disturbance, dehydration and relative oxygen depletion in the heart, brain and muscles from hyper-excitation. Successful management starts with rapid assessment of the clinical severity and safety in the immediate environment. While a talk-down approach may be useful for those mild cases without a toxicological cause, it might not work at its best and could be dangerous in those intoxicated cases. Team approach with adequate manpower was fundamental for safe and rapid control of the agitated. Chemical restrain should be initiated rapidly after physical restrain. The recommended first-line agent is benzodiazepines because of its safety profile particularly in the setting of stimulant overdose. Anti-psychotics may be used as a rescue therapy in patients without contra-indications like hyperthermia. Ketamine is currently under trial particularly in the pre-hospital setting. Second-line treatment e.g. propofol and intensive care should be considered in severe cases with fever and not rapidly responding to the first-line treatment. Cooling should be initiated for febrile patients as the severity and duration of hyperthermia associate with subsequent fatality. While researches are ongoing to find the best chemical restrain drug, the published studies included samples over-represented by alcohol intoxications. It is questionable if their results can be generalized to other toxicological causes of acute delirium. An individualized approach based on the presenting toxidromes and clinical severity titrating with the initial response to treatment is advocated.

# Cluster of Acute Poisonings Associated with a Ketamine Analogue, 2-oxo-PCE

*Magdalene HY Tang[a], YK Chong[a,b], Candace Y Chan[a,b], CK Ching[a,b], CK Lai[a,b], YK Li[c], Tony WL Mak[a,b]*

*[a]Hospital Authority Toxicology Reference Laboratory, Princess Margaret Hospital, Hong Kong*

*[b]Chemical Pathology Laboratory, Princess Margaret Hospital, Hong Kong*

*[c]Accident and Emergency Department, Princess Margaret Hospital, Hong Kong*

Ketamine and phencyclidine are well-known drugs of abuse of the arylcyclohexylamine class, the backbone of which is used for the synthesis of new psychoactive substances (NPS). In October 2017, a cluster of acute intoxications was encountered where patients presented with ketamine-like toxidrome. Upon initial toxicology screening, however, neither ketamine nor other causative agents were detected in the patients' urine. Instead, an identified substance was consistently detected. Further investigations using gas- and liquid-chromatography mass spectrometry led to the identification of an arylcyclohexylamine analogue, 2-oxo-PCE. The present study reports the analytical and toxicological profile of this emerging NPS. Chart review found, in total, 56 cases of 2-oxo-PCE associated acute poisoning between October and November 2017. Laboratory analysis confirmed the presence of 2-oxo-PCE in the urine of all patients; nasal swab samples from three patients revealed the lone presence of 2-oxo-PCE. Urine bedside immunoassay for ketamine was found not to cross-react with 2-oxo-PCE. In 55% of the cases, other drugs of abuse were detected on toxicology analysis; whilst in the remainder, 2-oxo-PCE was used alone. The main clinical symptoms associated with sole 2-oxo-PCE use include impaired consciousness (84%), confusion (60%), abnormal behaviour (44%), hypertension (80%) and tachycardia (40%). Convulsion (16%) was also observed relatively frequently. Management was mainly supportive, whilst three patients required intensive care. All patients recovered uneventfully. In conclusion, frontline clinical and laboratory personnel should be highly vigilant in the lookout for 2-oxo-PCE, a dangerous emerging arylcyclohexylamine analogue.

## Availability and Accessibility of Antidotes in Acute Hospitals

*Dr. Raymond S.M. Wong, Prince of Wales Hospital Poison Treatment Centre, Hong Kong*

Antidotes are important in the care of poisoned patients. They can reduce morbidity and mortality when used in a timely and appropriate manner. The stocking of adequate quantities of antidotes which allows them to be available within an appropriate timeframe is critical to ensure appropriate care of poisoned patients. For example, antidotes for conditions such as poisoning by an opioid, cardiac glycoside, or cyanide may be lifesaving if administered before irreversible injury occurs. They should be stocked in a location that allows immediate availability. In the public hospitals in Hong Kong, antidotes are classified into three levels which they needs to be available in all hospitals with Accident & Emergency Department (AED), at cluster level and central level respectively. The list is under regular review to ensure the antidotes are available with adequate quantities at appropriate timeframes. Further improvement is also under development to improve the accessibility of those agents which should be administered immediately.

## Acute and Late Complications of Chemical Warfare Agents

*Prof. Reza Afshari, Mashhad Medical Toxicology Centre (MMTC), Iran*

*Introduction:* Chemical Warfare Agents (CWA) including sulphur mustard gas were used against both Iranian soldiers and civilians during the Iran-Iraq War of 1980-88, by the regime of Saddam Hussein. This presentation aims at discussing 30 years of observing clinical manifestations and management of patients including successes and failures in both military and civil setting from this unique tragedy.

*Methods:* Literature reviewed via PubMed in spring, 2016. Personal experience and data are also discussed.

*Results: Acute effects following exposure;* Ocular findings including conjunctivitis, edema of the eyelids and closure of the eyes were observed in the majority of the cases. Cutaneous manifestation including erythema, blisters and hyperpigmentation were common. Dyspnea and wheezing were the most frequent respiratory manifestations.

*Delayed* effects; Skin disorders (itching, burning sensation, blisters, dry skin, dermatitis and pigmentary changes), pulmonary findings (dyspnea, cough and expectorations and various obstructive and restrictive lung diseases) and ocular problems (photophobia, red eye, tearing, corneal ulcers and blindness) form the most prevalent chronic and delayed complications.

Despite the earlier reports rejecting additional cancerogenic effects in this population, the relative cancer risk has been reported to be 1.7 to 4% *two decades* after the exposure, which is significantly higher than the average cancer risks. Other complications ranged from genes dysregulated and teratogenic effects to negative changes in civilian mental health are also discussed within the literature. Although standardized treatment plans exist, none of which are curable. Immediate preventive measures after exposure improve the following outcomes and supportive and symptomatic treatments for chronic manifestations are still the core of treatment plans, 30 years after the exposure.

*Conclusion:* Available human (soldiers and civilians) data from Iraq-Iran war, as the sole source of information on acute exposure to CWA, should be used for research and educational purposes. Chronic (i.e. respiratory) and delayed (i.e. cancer) manifestations related to exposure to CWA is still evolving as the victims are getting aged and minor risks could become more prominent in future. Management of CWA victims should be integrated into the current curricula of medicine and health. [This presentation would include graphical images from CWA victims]

*References:*

1. Panahi Y, Gholami N, Ghojazadeh M, Moslemi F, et al. Complications and Carcinogenic Effects of Mustard Gas--a Systematic Review and Meta-Analysis in Iran. Asian Pac J Cancer Prev. 2015; 16(17): 7567-73.

2. Balali-Mood M, Afshari R, Zojaji R, Kahrom H, Kamrani M, Attaran D, Mousavi SR, Zare GA. Delayed toxic effects of sulfur mustard on respiratory tract of Iranian veterans. Hum Exp Toxicol. 2011 Sep; 30(9): 1141-9.

## Medicines Discovery, Development and Evaluation

*Prof. Juliana C.N. Chan, The Chinese University of Hong Kong, Hong Kong*

According to the World Health Organization, 70% of all deaths are related to noncommunicable disease (NCD) including diabetes, cancer, cardiovascular and respiratory diseases which are often associated. With aging and increasingly young onset of these NCDs, multiple morbidities are now major challenges in our healthcare system. While medications are armamentarium in our prevention and control of many diseases, notably NCD, their delayed, excessive and inappropriate usage can lead to adverse clinical outcomes. Rapid technological development and genomic research offer new avenues for discovery of human-relevant drug targets while inter-ethnic differences in pharmacokinetics and pharmacodynamics may influence dosing regimen in order to maximize benefits and minimize harm.

With the digitalization of medical informatics, administrative databases and registers are now used to evaluate effectiveness of medications, complementary to clinical trial efficacy data. At the same time, these real world evidence can identify unmet needs and detect interactions between subphenotyes and treatment responses. To achieve these interlinking tasks, there is a need to improve the practice environment to ensure that patients have early access to assessment and effective medications with ongoing support to promote treatment adherence and self management in order to bring out the best of clinical expertise and technological advancement. It is against this background that these technological developments must be paralleled by the development of clinical pharmacology and toxicology, along with other specialties, to ensure the scientific, safe and effective use of medicinal products for prevention of hospitalization, disabilities and premature death.

# Therapeutic Drug Monitoring in Clinical Toxicology and Drug Safety

*Prof. Reza Afshari, Mashhad Medical Toxicology Centre (MMTC), Iran*

*Therapeutic Drug Monitoring (TDM)* is defined as the quantification and interpretation of drug concentrations in blood to optimize pharmacotherapy. TDM is focused on first, inter-individual variability of pharmacokinetics, and second on population at higher risk including children, pregnant women, elderly, etc. TDM is more important for drugs with narrow therapeutic windows that include but not limited to antiarrhythmics (e.g. digoxin), antibiotics (gentamicin), anticancers (methotrexate), anticonvulsants (phenobarbital), antidepressants (amitriptyline), antipsychotics (clozapine), bronchodilators (theophylline), immunosuppressants (azathioprine), mood stabilizers (lithium), etc.

*In clinical toxicology*, some aspects of TDM are unique such as pharmacokinetics drug interactions (PKI) in exposure to *high doses* where specific information is less available, pharmacodynamics interactions in overdose with or without PKI, high dose effects as opposed to therapeutic side effects, acute and acute on chronic pharmaceutical poisonings, toxicity of metabolites in comparison with the drug itself, self-supra-therapeutic use of mediations, patients with substance use (tolerance and withdrawal), intravascular redistribution, etc. (see main text).

*Drug safety and pharmacovigilance* in a wider view (in this paper) include a system to detect, collect, assess, prevent and control adverse effects of pharmaceutical products that include TDM. These adverse effects could be picked up during drug development phases (animal studies, patients and healthy volunteers) and also is extended to after introducing medications to pharmaceutical market.

*In medical toxicology wards*, a distinctive field of research exists to evaluate certain side effects that are observed in "human subjects" only in "overdose settings", which is not possible to study during drug development processes or when medications are in use among populations. --- An experience of co-proxamol (dextropropoxyphene and paracetamol) withdrawal from the pharmaceutical market will be discussed.

In conclusion, medical and clinical toxicologists need to develop a separate set of educational materials dedicated to therapeutic drug monitoring and drug safety in *overdose*settings.

*References:*

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2. Bateman DN, Afshari R. Co-proxamol and suicide: Licence needs to be changed. BMJ 2003; 327(7409): 287.

## Antidotes for Opioid Poisoning

*Dr. Jou-Fang Deng, National Poison Center, Taipei Veterans General Hospital, Taiwan*

Opioid addiction has been existed as an unsolvable issue in both the medical and social aspects since many hundred years ago. It could be resulted from either a chronic use of high-dose or extended-release opioids for pain control or a chronic abuse of the opioids. In United States, overdose deaths involving opioids have increased fivefold since 1999. The rate of drug overdose death involving synthetic opioids nearly doubled between 2013 and 2014, the category includes both prescription synthetic opioids (e.g., fental and tramadol) and non-pharmaceutical fentanyl manufactured in illegal laboratories (illicit fentanyl). In 2016, opioid overdoses killed more than 42000 people. The USA-CDC notes that heroin and fentanyl are most often used in combination with other drugs, such as cocaine, or alcohol, which increases the risk of overdose. The presence of hypopnea or apnea, miosis and stupor should lead the clinician to consider the diagnosis of opioid analgesic overdose. Naloxone is a competitive mu opioid-receptor antagonist that reverses all signs of opioid intoxication. It is active when the parenteral, intranasal, or pulmonary route of administration is used. The onset action is less than 2 minutes (IV), however, the duration of action is 20-90 minutes only, a much shorter period than that of many opioids. Dosing of naloxone is empirical. The effective dose depends on the amount of opioid analgesic the patient has taken or received, the relative affinity of naloxone for the mu opioid receptor and the opioid to be displaced, the patient's weight and the degree of penetrance of the opioid analgesic into the CNS. The initial dose for adults is 0.4 mg; if there is no response, the dose should be increased every 2 minutes, to a maximum of 15 mg. If there is no abatement in respiratory depression after the administration of 15 mg, it is unlikely that the cause of the depression is opioid overdose. Reversal of opioid analgesic toxicity after the administration of single doses of naloxone is often transient; recurrent respiratory depression is an indication for a continuous infusion. Due to the significant increase of the ED visit and death related to opioid overdose, the prehospital resuscitation of using naloxone was worthwhile to be implemented. Currently, there are three USA FDA-approved formulations of naloxone: Injectable (professional training required), autoinjectable and prepackaged Nasal Spray. EVZIO® is a prefilled auto-injection device that makes it easy for families or emergency personnel to inject naloxone quickly into the outer thigh. Once activated, the device provides verbal instruction to the user describing how to deliver the medication, similar to automated defibrillators. NARCAN® Nasal Spray is a prefilled, ready to be used by the patient or family members, needle-free device that requires no assembly and is sprayed into one nostril while patients lay on their back. Both NARCAN® Nasal Spray and EVZIO® are packaged in a carton containing two doses to allow for repeat dosing if needed. They are relatively easy to use and suitable for EMS and home use in emergency situations.

## Management of Venomous Snakebites

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There are 4 families of venomous snakes in the world, but *Elapidae* and *Viperidae* are the majorities. Snake venoms are complex mixtures of several compounds including proteins, enzymes, vasoactive amines and other substances. The enzymes, such as phospholipase A2, hyadruronidase and hemorrhagin, cause local effects. They induce tissue edema, inflammation and necrosis. Systemic effects of venoms are hemostatic disorder, neuromuscular blockade and muscle injuries. Neprotoxicity and cardiotoxicity are also found in some venomous snakes. Venom of the snakes in *Elapidae* family contains toxin which causes neuromuscular blockade. *Viperidae* family snakes have venoms which cause hemostatic disorder. However, there is variability of the mixture in venom among snakes in the same family or even subfamily. At the same time, ratio of compounds in the venom of the individual snake is also not constant in different times. Thus, clinical feature of snake bite also varies among the cases.

Diagnosis of venous snake bite is mainly based on clinical features and its epidemiology. Specific and rapid laboratory test to identify the snake is not available in general setting. There are 4-20% of the bites which are "dry bite" and no specific management is needed.

Though supportive care is the most important management of snake bite, antivenom, if available, will lessen, shorten or even abort some systemic effects of the venom. Antivenom is a specific antibody to snake venom. It is available in the form of either whole IgG, Fab or $Fab_2$. Specific monovalent to certain snake is a therapeutic of choice if diagnosis is able to pin down to a certain snake. Polyvalent is able to antagonize venom of several types of snakes and should be used in the cases which no definite snake are diagnosed. However, antivenom is not a magic bullet to treat the patients, because their adverse reactions should be considered. The incident ranges from 1-40% depending on types and their manufactures.

In principle, antivenom is able to bind and neutralize venom in the circulation, but not in extravascular compartments. Therefore, it will be indicated if certain degree of hematostasis disorder from the hematotoxin is detected. The dose is by titration basis. On the other hand, antivenom for neurotoxin should be administered as early as possible. It is recommended at the high dose to ensure its adequacy to neutralize existing venom. For local effects, antivenom therapy has not shown beneficial effect. Therefore, existing of local effect is not an indication for administering antivenom.

In summary, diagnosis of specific type of venomous snake should be made based on clinical presentation and epidemiologic data. Supportive treatment should be initiated since the early phase. Specific antivenom should be considered if available and indicated.

## Prevention of Hypersensitivity Drug Reactions

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Hypersensitivity drug reactions (HDR) refer to reproducible symptoms or signs initiated by exposure to a drug at a dose normally tolerated by non-hypersensitive persons. HDR belong to type B adverse drug reaction in the Rawlins and Thompson classification. These reactions are generally unrelated to dosage and less common, but they often cause more serious illness and even death. HDR occur in individuals with certain predisposition. They are not readily anticipated and thus considered difficult to prevent.

Immune- and nonimmune-mediated HDR can have similar inflammation and clinical presentation despite of different pathomechanism. It is important to understand and diagnose a suspected HDR on a concept of underlying pathogenetic mechanism. Failure to do so can lead to incorrect conclusions, inappropriate advice on prevention, and ineffective treatment. The diagnostic approach to HDR should include a detailed description on the drug history and clinical manifestations, and followed by skin testing, in vitro testing, and drug provocation testing.

Patients with a history of severe immune-mediated HDR must avoid the medication suspected to have caused the reaction. They should be educated which drugs or drug classes to avoid, and receive proper documentation about their drug allergies in order to prevent future exposure to culprit drugs. If there is a continued need for drug therapy, structural similarities between the culprit and the newly given drug should be avoided and a non-cross-reactive alternative drug given. When the only therapeutic option is the drug inducing the reaction (e.g. aspirin-exacerbated respiratory disease), temporary drug tolerance can be induced by desensitization.

The discovery of associations between HLA alleles and many severe cutaneous adverse reactions such as carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis in Han Chinese has created the promise for prevention through screening prior high-risk drug commencement.

## CME / CPE / CNE Accreditations

| **CME** | | |
|---|---|---|
| **Institution** | **Points** | **Category** |
| Hong Kong College of Anaesthesiologists | 5 | Non-ana |
| Hong Kong College of Community Medicine | 4 | |
| Hong Kong College of Emergency Medicine | 4.75 | Passive |
| Hong Kong College of Paediatricians | 5 | Cat. E |
| The Hong Kong College of Pathologists | 1 | pp |
| Hong Kong College of Physicians | 4.5 | |
| The Hong Kong College of Psychiatrists | 4.5 | pp/op |
| CNE: Pending | | |
| **CEU: 5 points accredited** | | |