Professor Bruno Megarbane

Bruno Mégarbane is Professor of critical care medicine at Paris-Diderot University and directs a research team at INSERM UMRS-1144. He is the Head of the Department of Medical and Toxicological Critical Care at Lariboisière Hospital, Assistance Publique – Hôpitaux de Paris, in Paris, France. He has conducted several clinical and experimental studies in clinical toxicology, mainly regarding mechanisms of opioid-related respiratory toxicity, prognostic factors of life-threatening poisonings, and management of refractory cardiotoxicant poisonings using ECMO.

Vulnerability to Understand and Limit Drug Toxicity

Bruno Mégarbane, MD, PhD.
Department of Medical and Toxicological Critical Care, Lariboisière Hospital, Paris-Diderot University, INSERM UMRS-1144, Paris, France.

Features of drug poisoning highly vary from one individual to another when considering an exposure to same drug amount. Individual vulnerability resulting in more severe presentations and possibly worse outcome is related to gene and non-gene factors and is related to both the pharmacokinetic and pharmacodynamic aspects of the poisoning. Variability may also result from drug-drug interactions in the multi-drug intoxications. The psychotropic drugs are probably responsible for the most marked interindividual variability (in comparison to the cardiotoxicants or the analgesics) due to the development of tolerance in the patients with previous long-term treatments. The pharmacokinetic variability of the poisoning presentation or time course may be due 1)- to alterations in the gastrointestinal absorption; 2)- to the drug tissue distribution like at the blood-brain barrier with an increasing role attributed to the membrane transporters; 3)- to the drug metabolism frequently in the liver and involving the different cytochromes P450 which activities can be selectively enhanced or inhibited; and 4)- to the drug elimination mainly in relation to the non-specific impairment in the liver and renal functions. The pharmacodynamic variability usually results from the receptor modulation either due to their membrane expression or their ability to transduce the message intracellularly. Such causes of individual variability are major issues to understand in the current opioid overdose crisis since the opioid dose is clearly not the only reason for the onset of severe poisoning or fatality. Investigation at the bedside of the different possible mechanisms of interindividual variability may appear challenging. However, simple readily available biological and analytical tests may be helpful to rapidly understand the time-course of the poisoning, select the adequate treatments and predict the final outcome. Calculating the drug metabolic ratio for is instance a direct indicator of the corresponding enzyme activity. Analysis of the relationships between the coma depth and the drug concentrations may also rapidly suggests the possible causes of variability in the psychotropic drug toxicity like drug-drug interactions or the onset of pharmacodynamic tolerance. The objectives of this presentation are to identify the causes of variability that are worthy to investigate at the bedside in order to improve the management and outcome of the poisoned patient.