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Reference

13. Clinical findings in patients receiving physostigmine in a toxicologic ICU: A quality and safety assessment study
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Objective: Physostigmine is a cholinergic drug that is used in reversal of anticholinergic syndrome (AChS). At our institution, physostigmine has been used for the last 20 years without severe adverse events. We decided to perform a retrospective quality assessment to judge the safety of our policy and to describe the clinical course of the patients.

Methods: We browsed the records of all patients admitted to our toxicologic ICU from January 2011 to December 2012, retrieving 151 patients having received physostigmine. We derived data about the presence of symptoms of AChS, the amount of physostigmine delivered, the clinical results and rates of potential side effects.

Results: In total 99 patients (65.5%) were judged as suffering from AChS by the treating physician. The remaining cases (n = 52) received physostigmine for reversal of more unspecific delirium or coma. The AChS-patients had the typical features of AChS more often than patients in the unspecific delirium group (e.g. 30% versus 20% for dry skin/mouth, 45 versus 20% reduced bowel movements, 56% versus 37% slurred speech, and 43% versus 28% agitation). The mean amount of physostigmine administered was 22.7 mg (95% CI ± 86.6) for the AChS group and 16.7 mg (95% CI ± 34.3 mg) in the unspecific coma group, respectively. In classic AChS, 90 of 99 (90.9%) patients experienced resolution of symptoms after administration of physostigmine, as compared to 38 of 56 (67.8%) of patients with non-specific coma. All patients but one survived. In the fatal case the patient had severe prothrombin depletion with a QTC of 660 ms, recurrent ventricular tachycardia and hypoxic brain damage after prehospital cardiopulmonary resuscitation. We found no significant bradycardia, atrioventricular block or other conductance disturbance during or after administration of physostigmine; the same was true for bronchorrhea and diarrhoea.

Conclusion: Physostigmine is delivered to our patients in an ICU setting with continuous monitoring in a bolus or infusion manner with bolus dosage about 2 mg and infusion rates of 0.5 to 2 mg/hour. Clinical signs such as bowel movement or grade of delirium guide the dosage and cessation. We consider symptomatic bradycardia with extremely broadened QRS complexes as unfavourable for administration of physostigmine. The administration of physostigmine according to our clinical routine protocol is safe for our patients. Side effects seem to be rare and their nature mild. Typical AChS responded well to physostigmine, and even two thirds of cases of nonspecific delirium or coma responded to some extent to this therapy.

14. Population pharmacokinetics of an Indian F(ab′)2 snake antivenom in patients with Russell’s viper bite
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Objective: There is limited information on the pharmacokinetics of antivenom. The aim of this study was to investigate the pharmacokinetics of an Indian snake antivenom in patients with Russell’s viper (Daboia russelli) envenoming.

Methods: Patient data and serial blood samples were collected from patients with Russell’s viper envenoming admitted to a single hospital in Sri Lanka. All patients received the Indian polyvalent snake antivenom manufactured by VINS Bioproducts Ltd. Antivenom concentrations were measured with a sandwich enzyme immunoassay. Antivenom concentration time data were analysed using the MONOLIX® version 4.2 (Lixoft, Orsay, France, www.lixoft.com). One, two and three compartment models with zero order absorption and first order elimination kinetics were assessed. Models were parameterized with clearance (CL), intercompartmental clearance (Q), central compartment volume (VC) and peripheral compartment volume (VP). Between subject variability (BSV) on relative bioavailability (F) was included to account for variations in antivenom dose. The effect of covariates (age, sex, weight, antivenom batch and pre-antivenom concentrations) were explored initially by visual inspection and then in model building.

Results: There were 75 patients with a median age of 57 years (40-70 years) and 64 were male. There were 510 antivenom concentration data points. A two compartment model with zero order absorption and linear elimination kinetics and a combined error model best described the data. The inclusion of BSV on F and weight on VC improved the model. The inclusion of pre-antivenom concentrations also did not improve the model. Inclusion of different batch numbers on BSV of F did not improve the model. The final model parameter estimates were CL 0.078 L/h, VC 2.2 L, Q 0.178 L/h and VP 8.33 L. The median half-life of distribution was 4.6 hours (90% percentiles 2.6-7.1 hours) and the half-life of elimination, 140 hours (90% percentiles 95-223 hours).

Conclusion: Indian F(ab′)2 snake antivenom displayed biexponential disposition pharmacokinetics, with a rapid half-life of distribution and a much longer half-life of elimination. This is consistent with previous small studies. The pre-antivenom venom concentrations did not appear to influence the pharmacokinetics
15. The use of digoxin-specific antibodies in chronic digoxin poisoning

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Objectives: Digoxin-specific antibodies (digoxin Fab) are used for the management of digoxin poisoning, however, the indications and dosage of digoxin Fab have not been clearly elucidated. This study aimed to examine the effects of digoxin Fab in chronic digoxin poisoning, and whether this related to dose or patient characteristics.

Methods: This was a prospective observational study of patients recruited through the New South Wales (NSW) Poisons Information Centre from September 2013 to October 2014. A standardised data form was used to enter patient information. Serum of patients treated with digoxin Fab was collected from hospitals in NSW and free digoxin assays were performed using ultrafiltration to separate free and bound digoxin. The digoxin concentration was measured using the Multigen Digoxin assay. Free digoxin Fab was measured by enzyme immunoassay.

Results: There were 27 patients with chronic digoxin poisoning treated with digoxin Fab. The median digoxin and potassium concentrations were 4.7 mmol/L (3.6 µg/L) (interquartile range [IQR] 3.3 to 6.1 mmol/L) and 5.9 mmol/L (IQR 4.6 to 6.6 mmol/L), respectively. All but two patients had renal impairment with a median serum creatinine of 232 µmol/L (IQR 153 to 306 µmol/L). The median change in potassium and heart rate (HR) post digoxin Fab were 0.2 mmol/L (IQR -0.2 to 0.7 mmol/L) and 10 beats/min (IQR 4 to 21), respectively. The median dose of digoxin Fab used was 80 mg (IQR 40 to 80 mg). Bradycardia or slow atrial fibrillation (HR < 60/min) were the commonest presenting rhythms with a median HR of 44 beats/min (IQR 30 to 58). Digoxin Fab was not found to be effective in 16/27 patients (59%) (i.e. HR < 45/min and raised by 10 beats/min within 4 hours of digoxin Fab administration). There were 18 patients recorded to be taking regular beta-blockers or calcium antagonists, 20 patients were taking either spironolactone or angiotensin blocking agents. Gastrointestinal symptoms were present in 14/27 patients (52%). Six patients died in this series, none of the deaths was attributed to digoxin poisoning. Free and total digoxin concentrations and free digoxin Fab were measured in five patients. Free digoxin concentration dropped to almost zero within 1 hour of administering digoxin Fab.

Conclusion: In this study of chronic digoxin poisoning, digoxin Fab was not found to be effective in managing bradyarrhythmia. Other medications and diseases often contributed to bradyarrhythmia and hyperkalaemia and this likely explains the lack of response despite the rapid reduction in free digoxin caused by digoxin Fab.

Reference