Title: PHARMACOKINETICS OF INTRAVENOUS NALOXONE IN HEALTHY VOLUNTEERS

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Introduction. Naloxone is an antagonist used for reversal of unwanted side-effects of opioid agents. Its use in treatment of shock states has been recommended. The clinical effects of the drug have a short half-life after bolus injection, and intravenous infusions have been suggested as a means of obtaining a more prolonged action. Previous pharmacokinetic studies of naloxone have been undertaken using either radioimmunoassay, which cross-react with metabolites, or radioactive-labelled drug, a relatively insensitive method. The present study was carried out to investigate the pharmacokinetics of naloxone in healthy individuals using high pressure liquid chromatography for assay of serum concentrations.

Methods. Six male subjects, mean weight 77.7 kg (range 60-108) and mean age 31.2 years (range 28-34), and six female subjects, mean weight 59.0 kg (range 44-70) and mean age 25.8 years (range 22-28) were studied. Ethical Committee approval was obtained for the investigation. Following insertion of a 14 G cannula into a large vein in the antecubital fossa, naloxone 0.8 mg in 10 ml 0.9% saline was injected i.v. over a 30 sec period. Venous blood was sampled at 1, 2, 5, 10, 15, 20, 30, 40, 60. 90, 120, 150, and 180 min after naloxone administration had ceased. The samples were centrifuged and the serum stored at -70°C for subsequent analysis of naloxone concentrations using high pressure liquid chromatography and electrochemical detection. The naloxone was extracted from serum in dichloromethane, evaporated, redissolved in buffer, and injected on to the column. The serum naloxone-time data for each subject were analysed using weighted non-linear least-square regression analysis to fit bi- and tri-exponential equations. Pharmacokinetic parameters were derived using standard formulae. The significance of differences between groups was determined using the Wilcoxon rank sum test for non-parametric data.

Results. There were no significant differences between male and female subjects, and the results from all 12 subjects have been combined. There was a rapid decay in serum naloxone concentration; more than 90% of the administered dose had left the serum by 5 min (Figure). There were transient increases in serum concentrations, similar to those reported after the administration of fentanyl[1], at times varying from 20 to 90 min. Derived pharmacokinetic parameters are shown in the Table. None of the subjects experienced side-effects.

Discussion. In the present study, the terminal elimination half-life of naloxone in serum was 50 min less than that found for morphine in a previous study[2]. Clearance of naloxone was greater, and exceeds the hepatic blood flow, suggesting that hepatic metabolism is not its only route of elimination. The differences between the pharmacokinetic half-lives of naloxone and morphine and their clinical durations of action are probably related to lipid solubilities and receptor affinities rather than pharmacokinetic differences. The results of the present study demonstrate that wide individual variation occurs in disposition of naloxone within the body, but provide information which may be useful in the rational use of naloxone by infusion where such a method of administration is clinically appropriate.

References.

1. McQuay HJ, Moore RA, Paterson GMC, et al: Plasma fentanyl concentrations and clinical observations during and after operation. Br J Anaesth 51:543-549, 1979

2. Aitkenhead AR, Vater M, Achola K, et al: Pharmacokinetics of single dose i.v. morphine in normal volunteers and patients with end stage renal failure. Br J Anaesth 55:(in press), 1984

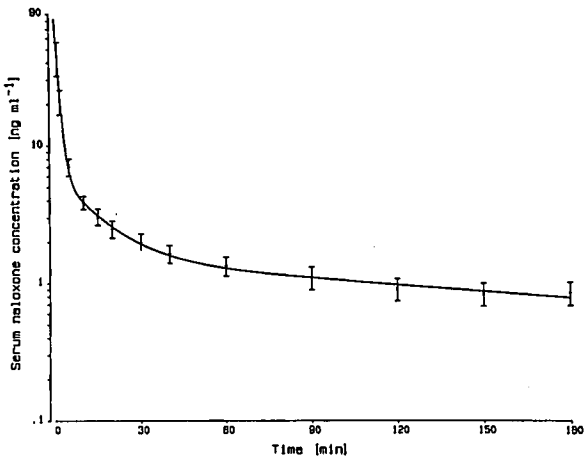
TABLE

Derived pharmacokinetic parameters

	Mean	Range
V_c	0.18	0.03- 0.38
V_d	5.36	2.16- 8.84
V_{ss}	3.65	1.43- 7.05
Cl	27.43	12.72- 54.62
$t_{1/2\beta}$	151.2	47.1 -313.2

V_c=apparent volume of the central compartment (l/kg); V_d=apparent volume of distribution (l/kg); V_{ss}=apparent volume of distribution at steady state (l/kg); Cl=total body clearance ($ml.min^{-1}.kg^{-1}$); $t_{1/2\beta}$=terminal elimination half-life (min).

FIGURE



Decay of serum naloxone concentration with time following administration of 0.8 mg naloxone i.v. to 12 normal subjects. Bars represent standard error of the mean.