NALOXONE PHARMACOKINETICS IN THE NEWBORN

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- 1 Plasma naloxone levels were determined by RIA over a period of 6–36 h in three groups of neonates, (1) those given 35 µg i.v. ($n=6$), (2) those given 70 µg i.v. ($n=6$) and (3) those given 200 µg i.m. ($n=17$) naloxone HCl within 1 min of birth.
- 2 After intravenous administration of 35 and 70 µg of naloxone peak levels of 4–15 ng/ml and 9–20 ng/ml respectively were reached in 5–40 min and the mean plasma half-life after both doses was 3.1 ± 0.5 h.
- 3 Peak levels of 7–35 ng/ml were reached 0.5 to 2 h after intramuscular administration of 200 µg. The fall in concentration after this was consistently biphasic with the levels declining rapidly between one and four hours and then slowly from four hours onwards.
- 4 Plasma levels at 24–36 h after i.m. administration were as high as they were 4 h after i.v. administration of 35 µg and this may account for the prolonged duration of action when this route is used.

Introduction

Despite the widespread use of pethidine and naloxone in the perinatal period, relatively little is known of their pharmacokinetics in the newborn.

Parenteral administration of naloxone to the newborn reverses the depressant effects of transplacentally acquired pethidine (Evans, Hogg & Rosen, 1976; Wiener, Hogg & Rosen, 1977; Gerhardt, Bancalari, Cohen & Rocha, 1977) but the duration of the reversal depends upon the route of administration used; intramuscular naloxone acts for 24–48 h compared with less than 90 min when the intravenous route is used (Wiener *et al.*, 1977; Brice, Moreland & Walker, 1979). Pethidine may persist in neonatal urine for several days after delivery (Cooper, Stephen & Aggett, 1977) indicating that the potential for pharmacological effects is present for some considerable time.

It has been suggested that the increased duration of effect of i.m. naloxone is either due to increased pethidine clearance when this route is used (Wiener *et al.*, 1977) or to the gradual release of drug from a depot at the site of injection (McGuigan & Mitchell, 1977). The present study was carried out to determine the plasma naloxone levels in neonates after i.v. and i.m. administration to examine the influence of dose and route of administration on plasma levels.

Methods

Patients

Babies born at term (37–42 weeks) after a normal pregnancy, labour and delivery were included in the study and informed consent was obtained from parents before labour was established. The mothers had received 50–150 mg (mean $\pm$ s.d., 108 ± 19 mg) pethidine intramuscularly up to 4 h (mean $\pm$ s.d., 1.55 ± 0.80 h) prior to delivery. Some also had epidural bupivacaine, lignocaine infiltrated into the perineum or nitrous oxide. After delivery venous blood was obtained from the umbilical vein, except in a few cases in the i.m. group when a mixture of venous and arterial blood was collected from the severed cord.

The newborn were given naloxone HCl via the umbilical vein or into the thigh muscle within 1 min of birth: six received 35 µg (1.75 ml Narcan Neonatal) i.v., six received 70 µg (3.5 ml Narcan Neonatal) i.v., and 17 were given 200 µg (0.5 ml Narcan) i.m. After i.v. administration the umbilicus was 'milked' to facilitate the entry of the drug into the general circulation. A maximum of seven heel-prick blood samples were collected at intervals over the next 6–36 h. The blood was collected in lithium-heparin tubes, centrifuged and the plasma stored at -20°C until assayed for naloxone.

Naloxone radioimmunoassay

The antiserum, supplied by Dr G.W. Aherne, University of Surrey, was produced in sheep against N-succinyl-normorphine-BSA. A final dilution of 1:26 bound 30% of a tracer amount of [3 H]-naloxone HCl (New England Nuclear, 58.8 mCi/mg) and this was used in the assay. Fifty seven picograms of [3 H]-naloxone HCl in 150 μ l 0.05 M phosphate buffer, pH 7.4, was added to each assay tube, with 200 μ l standard/unknown and 150 μ l antiserum. The reagents were mixed and incubated at 20°C for 50 min followed by 10 min in iced water. Separation was carried out by adding 0.5 ml saturated ammonium sulphate solution, the tubes were mixed, and after 30 min were centrifuged at 3000 g for 10 min. The supernatant was discarded and the precipitate washed by adding 0.5 ml 50% saturated ammonium sulphate solution, mixing and centrifuging. After discarding the supernatant, the pellet was dissolved in 0.5 ml water and transferred to a counting vial. A further two 0.5 ml aliquots of water were used to rinse the tube contents into the vial before counting in a liquid scintillation counter.

The displacement of [3 H]-naloxone label from antibody by naloxone standards is shown in Figure 1. The limit of sensitivity of the assay was 1 ng/ml with a coefficient of variation of less than 10% over the concentration range of 1–50 ng/ml. Naloxol, a metabolite of naloxone, synthesized by the method of Malspeis, Bathala, Ludden, Bhat, Frank, Sokoloski, Morrison & Reuning (1975), also displaced [3 H]-naloxone from the antibody but no significant inhibition of binding was caused by pethidine, oxytocin or bupivacaine (Figure 1).

Pharmacokinetic and statistical analysis

The plasma naloxone half-life after i.v. administration was calculated for each baby from the slope of the regression line fitted to the terminal portion of the logarithm of the concentration versus time curve by the method of least squares. Volume of distribution and clearance were calculated using the zero time plasma concentration determined by back-extrapolation of this line and the individual weight-related dose of naloxone.

After i.m. administration, the mean plasma naloxone concentrations at each of the sampling times were calculated, weighted according to the reciprocal of their variance and fitted to two pharmacokinetic models using the non-linear least squares regression programme FUNFIT (Pedersen, 1977). Model I assumed first order absorption and one-compartment distribution. Model II was similar to this but absorption was preceded by a two-compartment type model to represent drug precipitation and dissolution at the site of injection

Figure 1 Inhibition of binding of [3 H]-naloxone to antiserum by naloxone (■), naloxol (○), bupivacaine (△), oxytocin (●) and pethidine (□). Concentration causing 50% inhibition shown in nmol/l.

(Kostenbauder, Rapp, McGovern, Foster, Perrier, Blacker, Hulon & Kinkel, 1975).

Tests of statistical significance were carried out using the variance ratio (*F*-distribution) and Student's *t*-test (Goldstein, 1964).

Results

Figure 2 shows the plasma concentration in the six babies given 70 μ g i.v. naloxone. The mean ($\pm$ s.d.) peak plasma concentration and the concentration at 4 h in babies given 70 μ g intravenously, 13.7 $\pm$ 4.8 and 5.5 $\pm$ 3.3 ng/ml respectively, were higher than in those given 35 μ g i.v., 8.2 $\pm$ 4.9 and 2.2 $\pm$ 1.4 ng/ml respectively, the difference in the 4 h concentrations being statistically significant, $P < 0.05$. The mean plasma half-life, apparent volume of distribution and plasma clearance were similar in the two groups (70 μ g group: 2.65 $\pm$ 1.30 h, 1.78 $\pm$ 0.73 l kg $^{-1}$ and 576 $\pm$ 372 ml kg $^{-1}$ h $^{-1}$ respectively; 35 μ g group: 3.53 $\pm$ 2.20 h, 2.20 $\pm$ 1.18 l kg $^{-1}$ and 564 $\pm$ 488 ml kg $^{-1}$ h $^{-1}$). The time to reach peak plasma level was variable. In five cases peak levels were reached within 5 min of administration but in the remainder, plasma levels continued to rise for up to 40 min. After reaching a peak the plasma levels declined in a biphasic manner typical of intravenous dosing in two cases but fell mono-exponentially in the majority of babies.

Intramuscular injection of 200 μ g naloxone resulted in peak levels of 7.4–34.6 ng/ml at 0.5–2 h (mean 1.2 h). The mean ($\pm$ s.d.) peak concentration, 18.6 $\pm$ 8.0 ng/ml, was significantly greater than that obtained after i.v. administration of 35 μ g, 8.2 $\pm$ 4.9 ng/ml, $P < 0.01$, but was not significantly greater than that found after 70 μ g i.v., 13.7 $\pm$ 4.8 ng/ml. After

Figure 2 Neonatal plasma naloxone levels in six babies after 70 μ g i.v.

Figure 3 Mean ($\pm$ s.e. mean) plasma naloxone concentration in 17 neonates after 200 μ g i.m.

reaching a peak the logarithm of the concentration v time curves for the babies given i.m. naloxone were consistently biphasic with the levels falling rapidly between 1 and 4 h and more slowly between 4 and 36 h.

The mean plasma levels observed in all 17 newborn given i.m. naloxone are shown plotted v time in Figure 3. The regression lines obtained using models I and II were both a significant fit to the i.m. plasma level data with model II, incorporating a drug depot at the site of injection, yielding the smaller weighted residual sum of squares. The variance ratio for the

two models, however, was not significant indicating that model II did not fit the data significantly better than model I.

Discussion

Naloxone is metabolised by glucuronide conjugation, N-dealkylation and reduction of the 6-ketone group (Fujimoto, 1969a, 1969b; Weinstein, Pfeffer, Schor, Indindoli & Mintz, 1971). The metabolites resulting from the first two routes of metabolism were not available to test for cross-reactivity with the antiserum used in the present study. The major metabolite, naloxone-3-glucuronide, would probably not be recognized by the antiserum due to the addition of a relatively large moiety to the drug molecule at a position remote from that used to link the BSA in preparing the immunogen. One of the other two metabolites, the reduction product, naloxol, did cross-react with the antiserum but it has been reported that naloxol is not a major metabolite in any species except the chicken and pigeon (Fujimoto, 1969a, 1969b) and is present in the urine of man in small amounts only and then only as the glucuronide conjugate (Weinstein *et al.*, 1971).

Orally administered naloxone in rats undergoes extensive first-pass hepatic metabolism (Weinstein, Pfeffer, Schor, Franklin, Mintz & Tutko, 1973). The use of the umbilical venous route of administration in

man might inadvertently reduce the bioavailability of the drug since as much as half of the venous flow from the umbilical cord passes through the liver before reaching the general circulation (Crelin, 1973).

The relatively long time to reach peak levels observed in some babies in the present study was probably due to the drug remaining in the umbilical vein for some time after injection. This would be expected to delay the onset and reduce the magnitude of the drug action.

The plasma half-life of naloxone in neonates after intravenous administration was two to three times longer than that reported for adults (Ngai, Berkowitz, Yang, Hempstead & Spector, 1976). This is probably due to a diminished ability of the newborn to metabolize drugs since naloxone is chiefly eliminated by conjugation with glucuronic acid (Weinstein *et al.*, 1971) and this metabolic pathway has been shown to be deficient for a number of drugs and endogenous compounds in the newborn (Morselli, 1976).

Intramuscular administration of 200 µg of naloxone resulted in higher plasma concentrations and a longer time to reach peak plasma level than either of the i.v. doses. At 24–36 h plasma levels were still as high as they were 4 h after i.v. administration of the standard 35 µg dose and this may be the explanation for the prolonged duration of

action of the drug when given intramuscularly. In view of the variability of time to peak, ultimate levels and of the short duration achieved by giving only 35 µg naloxone i.v., and in view of the late peak concentration when given i.m., further investigation is required to determine whether it would be an advantage to use both routes simultaneously with the higher i.v. dose so that both a reliable rapid onset and a prolonged action is achieved.

The prolonged high plasma levels after i.m. naloxone are consistent with the suggestion of McGuigan & Mitchell (1977) that a drug depot may be formed at the site of injection. The i.m. naloxone level data significantly fitted the model incorporating a drug depot, although statistically it was not possible to justify the adoption of this model over a simple first-order absorption, one-compartment model. Further studies with more frequent sampling and/or a greater number of individuals are required to determine which, if either, of these models is appropriate.

We are grateful to Professor Forrester Cockburn for making the i.m. part of the study possible and thank Dr G.W. Ahern for supplying the naloxone antiserum and for advising on the RIA procedure.

The work was supported by grants from the Wellcome Trust, Winthrop Laboratories, and the Tayside Area Health Board.

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(Received September 3, 1979)