MORPHINE CONCENTRATIONS IN PLASMA AFTER INTRAMUSCULAR ADMINISTRATION

L. LAITINEN, J. KANTO, M. VAPAAVUORI AND M. K. VILJANEN

SUMMARY

Plasma morphine concentrations were measured by a radioimmunoassay technique following the intramuscular administration of morphine 0.2 mg/kg body weight as a preoperative medication. The highest plasma concentrations were obtained about one hour after the administration of the drug and there was a sevenfold variation in these concentrations between individuals. For 24 hr following a single intramuscular injection, there were measurable quantities of morphine or its metabolites in the plasma. In healthy patients who were undergoing a therapeutic abortion, there was no correlation between pain relief and the plasma concentration of morphine.

As a result of the development of a radioimmunoassay technique accurate measurements of the plasma concentrations of morphine have been made following its administration in clinical dosages (Spector and Parker, 1970). Despite the widespread use of morphine, its pharmacokinetics have not been studied intensively. The aim of this work was to investigate the pharmacokinetics of the drug following intramuscular administration and to compare plasma concentrations of morphine with the degree of analgesia.

PATIENTS AND METHODS

Morphine hydrochloride 0.2 mg/kg body weight and hyoscine bromide 0.006 mg/kg body weight (Scopolamin, Orion) were given i.m. as a preoperative medication to three groups of patients. Group I consisted of 11 healthy patients (mean age 23 yr (SD 5), mean weight 61 kg (SD 8)) who were scheduled for therapeutic abortion by hysterotomy. Plasma morphine concentration was measured at 25-140 min after the administration of the drug immediately before the induction of general anaesthesia.

In Group II there were 31 healthy patients (mean age 25 yr (SD 5), mean weight 61 kg (SD 6)) scheduled for therapeutic abortion by dilatation and curettage. There were 13 women who were pregnant for the first time and 18 women who had 1-3 previous pregnancies. Plasma morphine concentrations were measured at 20-105 min after the drug injection immediately before dilatation of the cervix in order to insert the laminaria into the cervical canal one day before uterine curettage (always following a Hegar No. 7 dilator). The plasma concentration was compared with the degree of pain relief. Analgesia was assessed by means of a simple scoring system: 3—the patient did not move or complain; 2—the patient moved or complained; 1—the patient moved and complained when dilatation was performed.

Group III consisted of five healthy patients (mean age 27 yr (SD 7), mean weight 58 kg (SD 5)) who were scheduled for therapeutic abortion. Plasma morphine concentrations were measured for 24 hr (fig. 2) after the administration of the drug during the application of the laminaria one day before uterine curettage. No drugs other than hyoscine were used in addition.

Plasma morphine concentrations were determined by the Abuscreen-TM radioimmunoassay for morphine (3H) (Chemical Research Department, Hoffmann-LaRoche Inc.) (using 7,8-3H-dihydromorphine with a specific activity of 2.5 mCi/mg). The limit of the method in plasma is 10 ng/ml and it measures both free and glucuronide-conjugated morphine. The reproducibility of the method is ±10%.

RESULTS

Individual plasma morphine concentrations for patients in groups I and II are shown in figure 1. The highest plasma concentrations were found about 1 hr after the i.m. administration of morphine. At this time the plasma concentrations varied over a
Fig. 1. Individual plasma morphine concentrations after the i.m. injection of morphine hydrochloride 0.2 mg/kg and hyoscine 0.006 mg/kg body weight. * = Group I, results 25–140 min after the drug administration. • = Group II, results 20–105 min after the drug administration.

sevenfold range. The plasma morphine concentrations for patients in group III are shown in figure 2. The peak plasma concentrations were found at 0.5–2 hr. Thereafter the concentrations decreased rapidly. At 24 hr only small or unmeasurable amounts of morphine were present in the plasma. For both the primiparous and multiparous patients in group II, there was no correlation between plasma morphine concentration and pain relief during cervical dilatation (regression analysis: \( b = 0.000348 \) and 0.000325 respectively).

Fig. 2. Individual plasma morphine concentrations in five patients in Group III. Morphine 0.2 mg/kg and hyoscine 0.006 mg/kg body weight.

DISCUSSION
The rate of absorption of a drug from an intramuscular site of injection varies considerably. Large variations in the plasma concentrations of diazepam, lignocaine and digoxin have been observed after i.m. administration (Ryden and Werkö, 1971; Kanto et al., 1974; Steiness, Svendsen and Rasmussen, 1974). In the present study a similar wide variation in plasma drug concentrations was found in different individuals. One hour after an i.m. injection, the plasma morphine concentrations varied sevenfold. Variations in the muscular circulation, the locus of injection, and the pH of the site of injection may have affected the rate of absorption of morphine.

Following the peak plasma concentrations obtained at 0.5–2 hr in group III, the values decreased relatively rapidly up to 6–8 hr. Twenty four hours after the injection only small amounts of morphine or its metabolites were detectable. However, toxicity resulting from accumulation of these compounds in blood may occur with repeated injections of morphine (Spector and Vesell, 1971).

Morphine is metabolized mainly by conjugation as glucuronide. N-demethylation is only a minor route of metabolism (Brunk and Delle, 1974). Our method measures both free and conjugated morphine and probably the N-demethylated metabolites also. Morphine and hyoscine have synergistic hypnotic and narcotic actions. For these reasons it is understandable that no relationship was observed between plasma morphine concentration and pain relief in this study. A better correlation may be possible between the plasma free morphine concentration and the analgesic activity in man since, following a single dose, the plasma free morphine concentration may reflect better the drug concentration in the brain (Way, 1968; Brunk and Delle, 1974). In animal studies a close relationship has been observed between the concentration of morphine in the brain and the degree of analgesia (Paalzow and Paalzow, 1971).

Our data suggest that for intramuscular medication before operation, morphine should be given about one hour before the induction of general anaesthesia.

REFERENCES
PLASMA MORPHINE CONCENTRATIONS


CONCENTRATIONS DE MORPHINE DANS LE PLASMA APRES ADMINISTRATION INTRAMUSCULAIRE

RESUME

On a mesure les concentrations de morphine par une technique de radio-immunologie après administration intramusculaire de morphine—à raison de 0,2 mg/kg de poids du corps—comme médication préopératoire. Les plus fortes concentrations de plasma ont été obtenues environ une heure après l'administration de la drogue et on a constaté des variations dans ces concentrations se multipliant jusqu'à sept fois suivant les individus. Pendant 24 h, après une seule injection intramusculaire, il y a eu des quantités mesurables de morphine ou de ses métabolites dans le plasma. Sur des opérées en bonne santé, qui étaient là pour subir un avortement thérapeutique, il n'y a eu aucune corrélation entre le soulagement de la souffrance et la concentration de morphine dans le plasma.

MORPHIUMKONZENTRATIONEN IN PLASMA NACH INTRAMUSKULARER VERABREICHUNG

ZUSAMMENFASSUNG


CONCENTRACIONES DE MORFINA EN EL PLASMA, DESPUES DE ADMINISTRACION INTRAMUSCULAR

SUMARIO

Se midieron las concentraciones de morfina en plasma siguiendo una técnica de ensayo de inmunización radial después de la administración intramuscular de morfina 0,2 mg/kg peso del cuerpo como una medicación preoperatoria. Se obtuvieron las máximas concentraciones de plasma una hora aproximadamente después de la administración de la droga y hubo una variación de siete divisiones entre individuos en dichas concentraciones. Durante las 24 horas que siguieron a una inyección intramuscular simple, hubo cantidades de morfina o sus rendimientos en la plasma. En pacientes sanos que estaban sufriendo un abordar terapéutico, no hubo correlación entre el alivio del dolor y la concentración de plasma de morfina.