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Placental transfer of flunitrazepam following intramuscular administration during labour

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After a single intramuscular dose of flunitrazepam 0.015 mg kg^{-1} ($n = 14$) in women 37 to 41 weeks pregnant, the concentrations in the umbilical artery and amniotic fluid were significantly lower than in maternal venous plasma. Although the difference between the maternal venous and umbilical venous plasma concentrations was not significant, the mean fetomaternal ratio was 0.7. The plasma protein binding of flunitrazepam was 80 ± 4% in the mother and 79 ± 5% in the umbilical circulation. Both mothers and midwives subjectively estimated intramuscular flunitrazepam as a valuable sedative—anxiolytic agent during the first stage of labour.

Keywords flunitrazepam placental transfer plasma protein binding clinical effect

Introduction

The primary aims of the use of benzodiazepines during labour are to ensure that the mothers are subjectively without fear and anxiety about the pain and other consequences of labour. In addition, these agents can relax the pelvic musculature, may decrease the amount of pethidine needed, and are able to inhibit eclamptic convulsions (Kanto, 1982). Flunitrazepam's prominent anxiolytic, sedative, and amnesic actions seem to be very useful during delivery (Kanto *et al.*, 1979a,b; Kanto, 1982). Furthermore, unlike other benzodiazepine derivatives, its placental transfer after a single maternal oral dose, both in early and late pregnancy, seems to be retarded (Kanto *et al.*, 1979b). These determinations were performed, however, about 12 h after the drug administration and, therefore, no final conclusions can be drawn about the time sequence of this phenomenon. In this study we have determined the placental transfer of flunitrazepam after intramuscular administration in labour in order to obtain more knowledge about the particular property of this benzodiazepine derivative.

Methods

After giving verbal consent, fourteen mothers received flunitrazepam (Rohypnol®, Hoffman-La Roche, Basle, Switzerland) 0.015 mg kg^{-1} intramuscularly as a sedative—anxiolytic agent during the first stage of labour (age 22–29, mean 26.3 years, weight 69–92, mean 72.3 kg, height 160–172, mean 166 cm). All mothers had an uncomplicated antenatal history and none was on drug treatment (except iron salts and vitamins). The duration of pregnancy varied between 37 to 41 weeks. No other parenteral or oral medication than flunitrazepam was used during the delivery.

The concentrations of flunitrazepam were determined by gas chromatography using Ni^{63}-

electron capture detector as described by Kangas (1977) for the determination of nitrazepam (direct method). The recovery percentage of this method is 99.1 ± 5.7 (s.d.) (n = 10) for plasma flunitrazepam and the lower limit of sensitivity is 0.2 ng ml^{-1}. The coefficient of variation in 10 determinations on the same day is 8.8%. The method is as useful in determining flunitrazepam concentrations in amniotic fluid, too. The plasma protein binding of flunitrazepam in the maternal and umbilical venous plasma was determined by equilibrium dialysis as described in our earlier studies on lorazepam's kinetics during labour (Kanto *et al.*, 1980). In addition, mothers and midwives estimated some drug effects during the first stage of labour according to the alternatives shown in Table 2.

Statistical analysis was carried out by Student's t-test (paired data).

Results

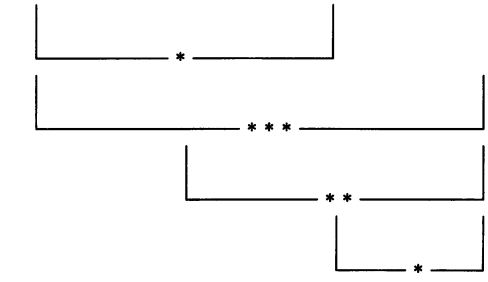
The simultaneous concentrations of flunitrazepam in the fetomaternal unit after a single 0.015 mg kg^{-1} maternal intramuscular injection can be seen in Table 1. The plasma protein binding of flunitrazepam was 80 ± 4% in the mother and 79 ± 5% in the umbilical circulation. The opinion of the mothers and midwives of the drug's effectiveness was favourable (Table 2). All except one (6 at 1 min) Apgar scores at 1 and 5 min were 8 or better.

Discussion

The present results confirm our earlier findings on the peculiar kinetic properties of flunitrazepam during labour (Kanto *et al.*, 1979b). The

Table 1 The plasma concentrations of flunitrazepam following a single 0.015 mg kg^{-1} intramuscular injection of the drug to the mother during the first stage of labour.

Patient	*Time (h)*	*MV (ng ml^{-1})*	*UV (ng ml^{-1})*	*UA (ng ml^{-1})*	*AF (ng ml^{-1})*
1	1.3	2.4	0.9	0.5	n.d.
2	1.6	1.9	1.3	1.2	n.d.
3	1.6	2.4	2.0	2.3	0.6
4	1.7	1.6	0.9	0.7	n.d.
5	1.9	2.5	2.4	1.0	0.2
6	2.8	0.5	0.4	0.4	0.2
7	3.3	0.6	0.3	0.2	n.d.
8	3.5	2.4	1.9	1.9	0.9
9	4.3	2.6	1.6	0.9	0.7
10	9.7	0.5	0.5	0.2	n.d.
11	10.3	2.2	1.0	0.4	0.3
12	11.5	2.2	2.6	2.7	1.0
13	11.5	2.1	0.9	0.8	0.4
14	11.5	1.3	1.1	0.8	0.2
Mean	5.5	1.8	1.3	1.0	0.3
s.d.	4.3	0.8	0.7	0.8	0.3



* = $P < 0.05$; * * = $P < 0.01$; * * * = $P < 0.001$
Time = hours up to the sample taking; MV = maternal vein; UV = umbilical vein; UA = umbilical artery; AF = amniotic fluid; n.d. = not detectable

Table 2 The opinions of mothers and midwives of the effectiveness of intramuscular flunitrazepam 0.015 mg kg^{-1} during the first stage of labour ($n = 14$)

Mothers' general opinion	*Midwives' general opinion*
Number of patients	*Number of patients*
Very good 3	1
Good 6	7
Moderate 4	5
Poor 1	1

Mothers' subjective sedative effect	*Mothers' subjective anxiolytic effect*
Number of patients	*Number of patients*
Marked 0	1
Moderate 4	7
Slight 8	6
Nil 2	0

Relaxing effect on the pelvic musculature (midwife)

Number of patients
Marked 1
Moderate 5
Slight 7
Nil 1

pharmacokinetics of this agent are described by a three-compartment open model and the elimination phase (half-life about 20 h) begins about 12 h after drug administration (Cano *et al.*, 1977; Kanto *et al.*, 1981; Kangas *et al.*, 1982). There is a close correlation between the drug effect and plasma concentration during the first 12 h after an oral drug intake (first and second compartments), but there never was a high correlation between clinical effect and the level in the third compartment (Cano *et al.*, 1977; Amrein *et al.*, 1979). The foetus is considered a 'deep compartment' (third compartment) which equilibrates slowly with the maternal compartment (Levy & Hayton, 1973). Thus, the foetal plasma concentrations could lag behind the maternal ones as the mother eliminates the drug (Kanto *et al.*, 1979b). The even lower levels in the amniotic fluid are in favour of this model. However, another possible explanation is rapid foetal tissue uptake of the lipophilic flunitrazepam which was reflected as the low umbilical levels of the drug.

Both patients and midwives considered intramuscular flunitrazepam as a valuable agent in decreasing anxiety during the first stage of labour. In this respect, it was thought to offer a good alternative to the routine use of diazepam.

In conclusion, due to the significantly lower levels in the fetal circulation, flunitrazepam seems to be a more useful derivative during pregnancy than other benzodiazepines (Kanto, 1982). This opinion is based, however, mainly on kinetic data and, therefore, neurobehavioural studies are warranted in this respect. Similarly, after a single maternal oral dose, the concentrations in the breast milk have shown to be lower than those in the maternal plasma (Kanto *et al.*, 1979b).

Our favourable opinion applies particularly to a single dose or intermittent use of flunitrazepam. Due to its long elimination half-life, flunitrazepam may accumulate in the fetus and milk during long-term treatment (Kanto, 1982). Thus high or repeated doses of this nitrobenzodiazepine derivative should be avoided during pregnancy and lactation.

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