Title: COMPARISON OF THE INTRINSIC AND SUBCUTANEOUS POTENCY OF NARCOTIC ANALGESICS

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Introduction. Knowledge of intrinsic potency of narcotics (defined as their analgesic concentration in whole brain) is necessary for the prediction of the pharmacological effects of these compounds, when administered parenterally, under pathological conditions that influence blood-brain permeability and thereby alter the brain concentration of narcotics. Information on the intrinsic potency of narcotics is also important for the prediction of the pharmacological effect of intrathecally administered narcotics,[1,2] when the influence of penetration from plasma to brain is eliminated. The present study was undertaken to compare the relative intrinsic and subcutaneous potencies of 3 widely used narcotics in rats. For sake of comparison the brain concentration of naloxone after s.c. injection was also investigated.

Methods. Groups of 8 to 12 Sprague-Dawley rats of both sexes weighing about 250 g were injected s.c. with about equianalgesic doses of 20 $\mu g \cdot g^{-1}$ $^{14}$C-morphine, 12 $\mu g \cdot g^{-1}$ $^{14}$C-meperidine, 0.04 $\mu g \cdot g^{-1}$ $^{3}$H-fentanyl and 0.1 $\mu g \cdot g^{-1}$ and $^{3}$H-naloxone in a total volume of 1 $\mu l \cdot g^{-1}$ body weight. About 25 min later the animals were lightly anesthetized with ether and at 30 min sacrificed by exsanguination through the abdominal aorta. The brains were removed and weighed and the heparinized plasma separated from the red cells. The radioactivity of aliquots of brain and plasma were measured in a Model 3375 Packard Liquid Scintillation Counter and their $dpm \cdot g^{-1}$ were calculated.

Results. The findings summarized in the table indicate that there was relatively little difference in the percentage (0.60 to 0.97) of the administered dose of the 4 compounds present in the plasma at 30 min. In contrast the percentage of the injected dose of morphine present in the brain at this time (0.013%) was much less than those of the other 3 compounds (0.193 to 0.500%) and the brain/plasma ratio of morphine 0.09±0.01, was 15 to 25 times lower than those of the other 3 compounds.

Discussion. Morphine, meperidine, fentanyl and naloxone are equally well absorbed into the plasma after s.c. administration. Morphine does not pass easily from plasma into the brain and only 0.013% of the total dose is present in the brain at 30 min. In contrast 15 to 38 times more of the other 3 compounds are in the brain at this time. If one assumes that the radioactivity present in the brain is proportional to the concentration of unchanged compounds and that the central nervous system effects of narcotics are related to their concentration in the whole brain, then on the basis of calculations shown in the table, the relative intrinsic potencies (morphine=1) of meperidine and fentanyl, 0.05 and 38 respectively, are much lower than their relative s.c. potencies, 1.66 and 500. Its high intrinsic potency might explain the severe respiratory depression observed after the intrathecal injection of small (0.05 to 1.0 mg) doses of morphine in man.[3,4]

| | Morphine | Meperidine | Fentanyl | Naloxone |
|---|---|---|---|---|
| Specific Activity ($Dpm \cdot 10^3 \cdot \mu g^{-1}$) | 5.0 | 4.2 | 6250§ | 2500 |
| Dose·g Body Weight$^{-1}$ ($\mu g$) | 20 | 12 | 0.04 | 0.1 |
| ($Dpm \cdot 10^3$) | 100 | 50 | 250 | 250 |
| Radioact. of Plasma ($Dpm \cdot 10^3 \cdot ml^{-1}$) | 20.4Π | 15.2 | 47.5 | 63.0 |
| % Total Injected* | 0.65 | 0.97 | 0.60 | 0.8 |
| Radioact. of Brain ($Dpm \cdot 10^3 \cdot \mu g^{-1}$) | 1.9 | 31.7 | 63.6 | 90.6 |
| % Total Injected | 0.013 | 0.500 | 0.193 | 0.2 |
| Brain/Plasma Ratio of Radioactivity | 0.09 | 2.18 | 1.36 | 1.4 |
| Drug Conc. in Brain† ($\mu g \cdot g^{-1}$) | 0.38 | 7.55 | 0.01 | 0.0 |
| Relative Intrinsic‡ Potency | 1.00 | 0.05 | 38 | — |
| Relative s.c. Potency | 1.00 | 1.66 | 500 | — |

*Plasma volume in rats 3.7% of body weight.
†Assuming that all radioactivity represents unchanged compounds.
‡Calculated from the ratios of the brain concentrations of the compounds.
§Because of small doses high specific activities had to be used.
ΠMean±SEM of 8 to 12 experiments.

References.
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