DURAL PERMEABILITY TO NARCOTICS: IN VITRO DETERMINATION AND APPLICATION TO EXTRADURAL ADMINISTRATION


SUMMARY

The permeability of cranial and lumbar dura to various substances including a number of narcotic analgesics was measured in vitro. Preliminary data on human postmortem material is reported. Permeability had a linear relation to the inverse of the square root of molecular weight. This is the expected relationship for a diffusion process dependent upon molecular weight. The differential mass selectivity coefficients for lumbar and cranial dura were calculated; they were similar at 0.8 and 0.9. This was greater than for diffusion in simple liquids, but much less than that for biological lipid membranes. This suggests that the low rates of diffusion are a property of the thickness of the dura rather than any inherent impermeability. A simple model for the dural transfer of drugs is described, and applied to narcotics. Its purposes were to suggest: the factors involved in the dural transfer of drugs; the physicochemical properties of drugs relevant to their dural transfer; worthwhile measurements in future studies. The model indicates that drug molecular weight and rate of absorption are important determinants of the efficiency of dural transfer. Low molecular weight and slow absorption produce high dural transfers. When applied to narcotics, these factors could produce a difference of up to an order of magnitude in the amount transferred directly across the dura.

The presence of opiate receptors in the spinal cord was the basis for the spinal (intrathecal and extradural) use of narcotics. Animal studies (Yaksh and Rudy, 1976; Yaksh et al., 1980), confirmed in man, show that analgesia (Wang, Nauss and Thomas, 1979; Magora et al., 1980), hormonal (Cowen et al., 1982) and side-effects (Reiz and Westberg, 1980) occur after spinal use. The nature and frequency of these effects indicate that spinal opiates do have specific regional activity.

There are more reports of extradural opiate use than of intrathecal use. The fate of drugs given extradurally is complicated (Bromage, 1975, 1981). The desired direct transfer of narcotic across the dura competes with uptake and removal by the extensive extradural venous blood flow and with reversible uptake into extradural adipose tissue. While local actions of narcotics outside the central nervous system (c.n.s.) have been described (Sastry, 1979; Mays et al., 1981), it is generally accepted that their principal actions are within the c.n.s. This is a critical difference from the extradural use of local anaesthetics.

The systemic availability of extradurally administered narcotics resembles that of the same dose given i.m. (Cousins et al., 1979; Weddel and Ritter, 1981). How much of this extradural narcotic is transferred directly across the dura? The magnitude of this transfer will determine the additional regional effect from extradural administration, and it is this additional regional effect which justifies the use of the procedurally elaborate extradural route for opiates.

In the first part of this study rates of transfer of a variety of compounds across human cranial and lumbar dural membranes were measured in vitro. The experimental aims were to obtain: physicochemical data on the nature of the dural membrane; an order of magnitude estimate for the transfer rates of narcotic drugs across the dura; and an estimate of the relative transfer rates that can be expected for different narcotics.

The second part of the paper presents a simple model which describes dural drug transfer. The
model is semiquantitative, allows discussion of the qualitative factors involved and is applied to extradural narcotics. Using in vitro data on dural permeability obtained experimentally, it provides a rational basis for choice of drug and of injection volume. Appropriate measurements are suggested which may be helpful in assessing the efficiency of dural transmission in pharmacokinetic terms. In particular, the model suggests reasons why the degree of dural transmission may vary between individuals. This variation may contribute to the wide range of analgesic effect which is such a feature of the clinical use of extradural narcotics.

METHODS
An apparatus suitable for the study of the transfer of compounds across the dura mater was designed and built in the Nuffield Department of Anaesthetics, John Radcliffe Hospital, Oxford. It consisted of two Perspex blocks each with a chamber of similar shape and volume (10 ml) which clamped together so that the chambers communicated through a port of fixed area (2.83 cm²). The whole device was kept at a given temperature using a temperature-controlled water bath (fig. 1).

![Fig. 1. Apparatus used for dural transfer experiments.](image)

The dura used in these experiments was obtained at postmortem from subjects with no history of neurological disorder and in whom there was no reason to suspect damage to the dural membranes. The specimens were washed to remove any blood and then frozen until required. Pieces of dura, both cranial and lumbar, were then cut to a size of approximately 4 cm² and placed over the port of one of the blocks. The other block was then screwed tightly into place by means of four locating screws. The chambers were filled with a quantity of Tris buffer (Tris-Cl 0.2 mol litre⁻¹, pH 7.4 at 37 °C).

The chambers always contained a final volume of 10 ml. The contents of the chambers were stirred throughout by means of a magnetic follower in each chamber. The apparatus was allowed to reach the required temperature before the experiment was started. An exact volume of a solution of the compound under test was then introduced to chamber 1 of the apparatus and immediately a sample (100 μl) was removed from chamber 2 at time 0. Further samples, again of 100 μl (to a total volume of 600 μl out of 10 ml without replenishment with buffer) were taken at 5-min intervals up to 25 min. The apparatus was washed thoroughly with Tris buffer between experiments.

A wide variety of compounds was studied: methanol, ethanol and propanol were measured by gas–liquid chromatography (Curry, Walker and Simpson, 1966); digoxin by radioimmunoassay using a kit obtained from Amersham International; glucose by an enzymatic glucose oxidase technique using a Beckman analyser; cortisol by competitive protein binding (Beardwell, Burke and Cope, 1968); fentanyl by radioimmunoassay using a kit obtained from IRE (UK) Ltd; morphine and diamorphine by radioimmunoassay using an antiserum from Guildhay antisera which cross-reacted with both drugs; methadone by radioimmunoassay using a label from Research Triangle Institute, a gift from the National Institute for Drug Abuse, and antiserum which was a gift from Prof. C. Inturissi; buprenorphine by radioimmunoassay (Bartlett et al., 1980); progesterone by radioimmunoassay using antisera obtained from Guildhay antisera and phenazocine by measuring its fluorescence in HCl 1 mol litre⁻¹ at an excitation wavelength of 284 nm and an emission wavelength of 310 nm.

Initial experiments used cranial dura from four individuals, and examined the variation in permeability of the dura to ethanol at different concentrations and temperatures. Further experiments examined the permeability of both cranial and lumbar dura obtained from a single individual to a variety of compounds. Three pieces of cranial dura (both meningeal and endosteal layers) were used, but only one piece of lumbar dura (just the meningeal layer) was available.

Initial concentrations of compound under study
were chosen to provide samples in the measurable range for each assay. The initial concentrations used were 10% (v/v) for the aliphatic alcohols, 100 μmol litre⁻¹ for the steroids and 0.1 mg ml⁻¹ for all the drugs except digoxin, for which the initial concentration was 0.01 mg ml⁻¹. These are comparable to reported initial concentrations for extradural narcotics varying from 10 mg ml⁻¹ for pethidine (Cousins et al., 1979) to 0.015 mg ml⁻¹ for fentanyl (Bullingham, McQuay and Moore, 1980). All experiments were performed in duplicate.

**Calculation of permeability**

The method of analysis was based on the Fick law of diffusion which states that diffusion flux is proportional to the concentration gradient.

\[
\text{Flux} = \frac{\text{constant} \times \text{area} \times \text{concentration gradient}}{\text{thickness}}
\]

\[
\dot{Q} = \frac{K \times A \times C_1 - C_2}{d}
\]

where

\( K = \text{constant} \)

\( A = \text{area} \)

\( C_1 = \text{concentration in chamber 1} \)

\( C_2 = \text{concentration in chamber 2} \)

\( d = \text{thickness of dura}. \)

In this experiment the concentration decrease in chamber 1 during the experiment was very small (in the worst case less than 2%). Thus the concentration gradient was equivalent to the initial concentration in chamber 1, and did not alter during the experiment.

\[
\dot{Q} = \frac{K \times A \times C_1}{d}
\]

The thickness, \( d \), cannot be known with certainty, but is constant for a given piece of dura. A new constant, the permeability \( P \), can now be defined:

\[
P = \frac{K}{d}
\]

Thus

\[
\dot{Q} = P \times A \times C_1
\]

or

\[
P = \frac{\dot{Q}}{A \times C_1}
\]

The total amount of substance which appeared in chamber 2 at each interval was plotted against time. The slope of this graph represents the flux of a compound through a given area of dura. Division by the area of the port (2.83 cm²) and the initial concentration in chamber 1 (\( C_1 \)) yields a value for the permeability.

\[
\text{Now} \quad P = \frac{\text{slope}}{2.83 C_1}
\]

This has the units of cm min⁻¹.

The thickness of the specimens of dura was measured at several separate sites with a micrometer. The nature of the material made such measurements only approximate.

**RESULTS**

In all experiments with all compounds tested on both lumbar and cranial dura, the appearance of substances in the low concentration side of the apparatus (chamber 2) was linear with respect to time, with correlation coefficients generally in excess of 0.98 for seven data points.

The experiments used either single pieces of dura from different subjects (tables I, II) or different

| Table I. Effect of concentration on the permeability of cranial dura to ethanol. Experiments carried out in duplicate at 37°C on cranial dura from four subjects. Results are mean ± SD. *Significant difference from 0.12 mol litre⁻¹ (P < 0.05, one-tailed Student's t test) |
|---|---|
| Ethanol concentration (mol litre⁻¹) | Permeability (cm min⁻¹) |
| 0.12 | 0.0048 ± 0.0010 |
| 0.24 | 0.0048 ± 0.0010 |
| 0.59 | 0.0048 ± 0.0009 |
| 1.15 | 0.0044 ± 0.0002 |
| 1.69 | 0.0040 ± 0.0004 |
| 2.20 | 0.0033 ± 0.0004* |

| Table II. Effect of temperature on the permeability of cranial dura to ethanol. Experiments carried out in duplicate at 0.59 mol litre⁻¹ ethanol using cranial dura from three subjects. Results are mean ± SD. *Significant difference from 37°C value (P < 0.01, one-tailed Student's t test) |
|---|---|
| Temperature (°C) | Permeability (cm min⁻¹) |
| 25 | 0.0050 ± 0.0002* |
| 30 | 0.0053 ± 0.0002* |
| 35 | 0.0061 ± 0.0001 |
| 37 | 0.0063 ± 0.0002 |
| 40 | 0.0069 ± 0.0002* |
| 45 | 0.0074 ± 0.0001* |
pieces of dura from the same subject (table III). The dispersion of the data was similar in each case, with an overall coefficient of variation of $8.7 \pm 2.2\%$ (SEM) in the former, and $12.5 \pm 2.7\%$ in the latter experiments. The experimental error was not significantly different for either type of experiment.

The dural permeabilities for experiments on cranial dura with varying ethanol concentration or temperature are shown in tables I and II. The permeability declined as the initial ethanol concentration increased to more than 0.6 mol litre$^{-1}$; this became statistically significant only when the initial concentration was 2.2 mol litre$^{-1}$. Permeability increased with temperature (table II); at 30 °C or less the values were significantly less than at 37 °C, and were significantly greater at temperatures of 40 °C or more.

Permeability of both cranial and lumbar dura to a variety of compounds is shown in table III. The results are displayed graphically in figure 2, where permeability plotted against $1/(\text{square root of molecular weight})$ produced a straight line relationship with a correlation coefficient of 0.97 for both cranial and lumbar dura. This is the expected relationship for a diffusion process dependent upon molecular weight. The permeability of lumbar dura was significantly greater than that of cranial dura by about 30% ($P < 0.05$, paired t-test). The thickness of cranial dura was about 0.5 mm and that of lumbar dura about 0.3 mm.

Fentanyl was excluded from the calculations, and from those for linear regression against molecular weight. Fentanyl had a permeability which, particularly for cranial dura, was about three times greater than expected for that molecular weight, with careful checking of the results and repetition of the experiment.

**DISCUSSION OF EXPERIMENTAL RESULTS**

Initial experiments on the permeability to ethanol of cranial dura from several subjects demonstrated that it was a saturable phenomenon (table I). When the initial concentration of ethanol increased to 2.2 mol litre$^{-1}$ the permeability was significantly reduced. This concentration is at least an order of magnitude greater than that likely to be found in the extradural use of narcotics. Typically, concentrations used are about 50 mmol litre$^{-1}$ for pethidine (Cousins et al., 1979) and 45 μmol litre$^{-1}$ for fentanyl (Bullingham et al., 1980). The permeability was also affected by temperature; there was an increase of 50% when the temperature increased from 25 to 45 °C (table II), which is consistent with a diffusion basis for the permeability.

The absolute permeabilities of compounds across both cranial and lumbar dura were low, but were of the order of 0.0015 cm min$^{-1}$ for compounds with molecular weights typical of opiate drugs. The permeability of the same compounds across the lumbar dura was generally similar to and usually greater than that for cranial dura (table III), which accords with the greater thickness of cranial dura. Excluding

<table>
<thead>
<tr>
<th>Compound</th>
<th>MW</th>
<th>Permeability (cm min$^{-1}$)</th>
<th>Cranial dura</th>
<th>Lumbar dura</th>
<th>Lumbar/cranial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>32</td>
<td>0.0060 ± 0.0005</td>
<td>0.0099</td>
<td>1.64</td>
<td></td>
</tr>
<tr>
<td>Ethanol</td>
<td>46</td>
<td>0.0059 ± 0.0006</td>
<td>0.0076</td>
<td>1.28</td>
<td></td>
</tr>
<tr>
<td>Propanol</td>
<td>60</td>
<td>0.0039 ± 0.0008</td>
<td>0.0063</td>
<td>1.59</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>180</td>
<td>0.0025 ± 0.0003</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>285</td>
<td>0.0015 ± 0.0001</td>
<td>0.0036</td>
<td>2.36</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>310</td>
<td>0.0012*</td>
<td>0.0014</td>
<td>1.16</td>
<td></td>
</tr>
<tr>
<td>Progesterone</td>
<td>315</td>
<td>0.0012 ± 0.0001</td>
<td>0.0011</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>Phenazocine</td>
<td>322</td>
<td>0.0015*</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Diamorphine</td>
<td>326</td>
<td>0.0014*</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>337</td>
<td>0.0061 ± 0.0017</td>
<td>0.0048</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>Cortisol</td>
<td>363</td>
<td>0.0016 ± 0.0001</td>
<td>0.0019</td>
<td>1.18</td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>468</td>
<td>NR</td>
<td>0.0004</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>781</td>
<td>0.0003*</td>
<td>0.0005</td>
<td>1.73</td>
<td></td>
</tr>
</tbody>
</table>
Fentanyl, which displayed aberrant behaviour, the trend was statistically significant.

There was a marked relationship between permeability of all the compounds tested and molecular weight (fig. 2). This relationship was seen over a wide range of molecular weights, from methanol (32 daltons) to digoxin (781 daltons). Lipophilicity was apparently not an important factor, as can be seen from the fact that morphine and diamorphine, which have very different lipid solubilities yielded similar permeabilities.

An exception to the general rule for molecular weight was fentanyl, which crossed cranial and lumbar dura faster than would be predicted from its molecular weight. The reasons for this are not clear. Fentanyl is a lipophilic basic opiate, essentially similar in terms of its lipophilicity and pKₐ values to some of the other opiates tested in this system. However, Lieb and Stein (1969) in their investigation of the behaviour of compounds in biological membranes, noted that some compounds (particularly trimethylcitrate) behaved in a similarly anomalous manner. They suggested that the relationship was more properly between diffusion rate and molecular volume rather than molecular weight. Most of the compounds tested have a shape which approximates to a sphere; fentanyl, in contrast, is an extended molecule. The enhanced permeability found with fentanyl may also apply to molecules with similar structures, such as phenoperidine. In addition, the discovery that fentanyl has aberrant behaviour in dural transfer experiments, without being able to explain that behaviour, implies that it would be worthwhile to investigate all opiate drugs for special dural permeability.

Lieb and Stein defined a parameter, the differential mass selectivity coefficient (sₓₓ), which is a constant characteristic of a membrane at a given temperature and describes numerically the property of any material for impeding diffusion. The value of sₓₓ is independent of thickness, and was obtained for dura by plotting the log₁₀ permeability against log₁₀ molecular weight relative to methanol. The sₓₓ value was the negative of the slope.

The values for lumbar and cranial dura obtained by this type of plot (fig. 3) were very similar at 0.8 and 0.9. This is interesting for two reasons. First, as lumbar and cranial dura have the same anatomical and biochemical structure, the values for sₓₓ should be identical; the fact that this result was obtained gives confidence in the experimental data. Second, the value obtained in these experiments was greater than that for diffusion in simple liquids (0.3–0.5), but much less than those calculated by Lieb and Stein for biological cell membranes (2.9–6.0), or for polymethyl acrylate (3.8) or natural rubber (1.1). The collagen and elastin fibres of dura form a much more open structure than a lipid cell membrane. However, the cranial dura was about 0.5 mm thick, and lumbar dura about 0.3 mm; this is much greater than for lipid membranes. The apparent low permeability of dura is then almost entirely a product of
Transfer of drug across the dura will be assumed to follow Fick's law of diffusion, as was found for in vitro dural samples experimentally.

It is assumed (all assumptions are examined for validity below):
(i) the dura has uniform thickness and diffusion properties;
(ii) intradural (c.s.f. and cord) drug concentration is at all times close to zero. Intradural drug concentration is then neglected with respect to extradural drug concentration, so that the concentration gradient for diffusion across the dura is determined solely by extradural drug concentration.

The mass flux of drug across the dura (mass per minute) is then:
\[
\frac{dQ}{dt} = P \times A \times C_{ex}
\]

where
\[
\begin{align*}
Q &= \text{quantity transferred (mass units)} \\
P &= \text{dural permeability (cm min}^{-1}). \text{(This term includes the thickness of the dura and corresponds to the values determined experimentally in vitro.)} \\
A &= \text{area of dura exposed to the drug (cm}^2) \\
C_{ex} &= \text{extradural drug concentration (mass per ml). (The relevant drug fraction is that which is unbound.)} \\
t &= \text{time (min)}
\end{align*}
\]

Systemic availability after extradural opiate use resembles that seen after i.m. absorption. The amount of drug remaining at the extradural site of administration may be represented by a first order rate process, giving:
\[
D_{ex} = D_0 \times \exp(-k_{abs} \times t)
\]

where:
\[
\begin{align*}
D_{ex} &= \text{dose of drug remaining at the extradural site of deposition (mass units) after time } t \text{ (min)} \\
D_0 &= \text{the initial extradural dose (mass units)} \\
k_{abs} &= \text{the absorption rate constant (min}^{-1})
\end{align*}
\]

Assuming also:
(iii) the relationship between extradural drug dose and extradural drug concentration is described by:
\[
C_{ex} = \frac{D_{ex}}{V_{ex}}
\]

its considerable thickness rather than any specific impermeability.

The dura used in these latter experiments came from a single subject. Further work will be required to widen these results to dural specimens from other subjects. The evidence here of experimental variation for a single or several dural specimens suggests that extension of the experiments would not grossly alter the estimates of narcotic permeability or their relative order.
where:

\[ C_{ex} = \text{extradural drug concentration} \]
\[ V_{ex} = \text{an extradural volume of distribution (ml).} \]

(In general, this volume could include such effects as binding and ionization of the drug.)

Then:

\[ C_{ex} = \frac{D_0}{V_{ex}} \times \exp \left( -k_{abs} \times t \right) \]

Substituting this into equation (1), integrating over all time, and assuming:

(iv) \( V_{ex} \) is not a function of time

then:

Total fraction of drug transferred directly across the dura,

\[ F_D = \frac{Q}{D_0} \]

\[ = P \times A \times \frac{1}{V_{ex}} \times \int_0^\infty \exp \left( -k_{abs} \times t \right) dt \]

\[ = \frac{P}{k_{abs}} \times \frac{A}{V_{ex}} \quad (2) \]

General features of the model

Note first that equation (2) separates into two terms:

(a) \( P/K_{abs} \): a ratio of rate factors for which the drug is a major determinant.

(b) \( A/V_{ex} \): a ratio of geometric factors for which the details of technique and the anatomy of the extradural space are major determinants, that is this is situation dependent.

Consider now the separate factors with the two terms:

(a) Drug-dependent terms

**Dural permeability, \( P \)**

High permeability gives high total transfers. Permeability is determined by:

**Molecular weight (MW)**. Increase in MW is a principal factor for decrease in permeability. Most of the commonly used opiates have very similar MW in the range 300–400 daltons. Lower MW opiates include morphine (MW 285), levorphanol (MW 257), and meperidine (MW 246.5).

**Molecular shape**. The dura may be much more permeable to extended molecules than to globular molecules of the same MW. Thus fentanyl (MW 336) shows an anomalously high permeability in comparison with phenazocine (MW 321) or even morphine (MW 285). Molecular shape may be a very significant property for high permeability.

**Lipophilicity**. Increase in lipophilicity should increase permeability for a given MW. This increase usually involves the attachment of large hydrophobic residues to a molecule. The concomitant increase in MW may offset the effect of increase in lipophilicity. Thus diacetylmorphine (MW 369) is much more lipophilic than morphine (MW 285) but still has a lower permeability.

**Degree of ionization**. Penetration of lipid barriers can only be achieved by un-ionized drug molecules.

\[ \text{pH} = \text{p}K_a + \log_{10} \left( \frac{[\text{concentration of protonated base}]}{[\text{concentration of free base}]} \right) \]

The narcotic solutions reported for extradural use have used dextrose or saline solutions and hence had minimal buffering capacity. The pH of these solutions should therefore have come rapidly to that of the extradural space (assumed to be approximately 7.4).

The apparent p\( K_a \) of the common narcotics (Benson, Kaufman and Koski, 1976) are in the range 7–10. Thus at pH 7.4, the major fraction of such narcotics will be in the ionized form. Change in the degree of ionization is most rapid at pH values close to the p\( K_a \). The effect of p\( K_a \) on permeability would then be greater with narcotics with p\( K_a \) values at the lower end of the range such as morphine (Benson, Kaufman and Koski, 1976), p\( K_a = 7.93 \), and meperidine (Benson, Kaufman and Koski, 1976) p\( K_a = 8.50 \).

The dural membrane is not primarily a lipid barrier like the cell membrane. Taken with the discussion of narcotic ionization above, this means that p\( K_a \) is likely to be of only minor significance for permeability.

The absorption rate constant \( k_{abs} \)

Low absorption rate constants (slow appearance in the systemic circulation) will give high total dural transfers. In essence, the extradural drug concentra-
tion is maintained for longer. The absorption rate constant is determined by:

**Lipophilicity.** Increase in lipophilicity could lead to two opposing effects:

(i) A more rapid transfer into blood and thus an increase in $k_{abs}$. This is the general correlation seen for the i.m. use of opiates (Bullingham, 1981).

(ii) Increase in non-specific binding (Hollt and Teschemacher, 1975). Uptake into extradural adipose tissue will reduce the concentration gradient for diffusion into the vascular system, and hence reduce $k_{abs}$.

The overall effect of lipophilicity could consequently be small. The presence of extradural adipose tissue is a cardinal distinction between this site and muscle. Moreover, the quantity of adipose tissue in the extradural space is likely to vary between patients. Even within the same patient it may vary in relation for example to age or diet.

This leads to difficulties in predicting the effect of lipophilicity on $k_{abs}$. It may, however, be determined pharmacokinetically in the clinical situation, which should resolve the relative importance of each of the above competing processes. The small difference between i.m. and extradural absorptions reported for meperidine and morphine suggests that the non-specific binding effect is of only minor significance. Increase in lipophilicity leads then to increase in $k_{abs}$ as with intramuscular use.

**Extradural blood flow.** High extradural blood flow removes extradural drug more rapidly and so increases $k_{abs}$. Two examples are:

(i) Pregnancy (or other large intra-abdominal tumour) increases extradural blood flow.

(ii) Extradural vasoconstrictors (e.g. adrenaline) are expected to reduce extradural blood flow. The end result of using vasoconstrictors may not, however, be straightforward. Drugs of low lipophilicity, such as morphine, already have a relatively small $k_{abs}$; a vasoconstrictor may then exert only a small additional effect. With highly lipophilic drugs, transfer of drug into fat may already be exerting a significant reduction in $k_{abs}$ which will outweigh the effect of a vasoconstrictor. Very significant effects may only be seen with vasoconstrictors when very lipophilic drugs are used in patients who have little extradural fat and high extradural blood flows.

### (b) Situation-dependent terms

**Dural surface exposed to drug, A**

High surface areas give high total dural transfers. The principles which underly the extent of spread of extradurally administered solutions are reasonably well understood (Atkinson, Rushman and Lee, 1977). Information established for local anaesthetics is here equally applicable to other extradural drugs. The principal determinant is the volume of injectate. Other factors include posture and patient-related variables such as age and height. One notable difference between extradural narcotics and local anaesthetics concerns the level at which the spinal theca ends (commonly taken as S2). Any narcotic placed below this level may be regarded as lost to direct dural transfer. There is little logic in the sacral administration of narcotics.

**Volume of distribution of extradural drug, $V_a$**

Small volumes give high total dural transfers. $V_a$ is an apparently simple factor, but is determined by a number of very complicated events.

The volume of distribution is certainly related to the volume of injectate: larger injectate volumes will give larger volumes of distribution. Large injectate volumes will also increase the dural area ($A$) exposed to drug, so that, within limits, the opposed effects of these two factors may be expected to cancel. This implies a certain degree of independence of the extent of dural transfer from the volume of extradural solution given. A similarity may be noted here with extradural use of local anaesthetics with which, above a certain concentration of the local anaesthetic, the effect is observed to be independent of volume of injectate (Bromage, 1975).

Local anaesthetics, however, also act on nerve bundles within the extradural space. Extradural narcotics must enter the neuraxis for their major effects. This difference means that $V_a$ may play a more fundamental role in the case of extradural narcotics and this is discussed below.

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**AN ESTIMATION OF THE FRACTION OF AN EXTRADURAL NARCOTIC DOSE TRANSFERRED DIRECTLY ACROSS THE DURA**

Morphine and buprenorphine have been chosen as examples because they represent extremes for lipophilicity and MW (table I). To estimate $F_D$ in equation (2), numerical values must be assigned to the parameters contained within it:
Permeability, $P$

The values used are those measured on a sample of human lumbar dura in vitro, as described earlier.

Absorption rate constant, $k_{abs}$

The plasma profile of morphine after extradural administration resembles that of an i.m. administration (Weddel and Ritter, 1981). The values used are those reported for i.m. morphine in five volunteers (Stanski, Greenblatt and Lowenstein, 1978).

Both i.m. (Bullingham et al., 1980) and extradural (Bullingham, McQuay and Moore, 1980) buprenorphine show very rapid systemic absorption. I.m. buprenorphine produced peak concentrations within 5 min of administration. Using the terminal half-life of buprenorphine, 300 min (Bullingham et al., 1982), an estimate for the absorption half-life of 0.55 min may be obtained. A range of 0.1–1.0 is also taken around this value.

Dural surface exposed to drug, $A$

In the adult (Collins, 1976) the weight of the spinal cord is about 30 g, and so its total volume will be about 30 ml. The total volume of c.s.f. in the spinal subarachnoid space is 25–30 ml. The combined volume of c.s.f. and cord is thus about 60 ml, and spans 25 vertebral segments, from the foramen magnum to S2, over a vertical distance of about 50 cm. The volume per vertebral segment is thus about 2.4 ml in a vertical height of 2.0 cm. This volume can be considered as a uniform right cylinder with dura covering the curved surface. Its radius, $r$, is given by:

$$\pi \times r^2 \times 2.0 = 2.4$$

that is,

$$r = 0.62 \text{ cm}$$

The dural surface area per vertebral segment is then:

$$2 \times \pi \times r \times 2.0 = 7.77 \text{ cm}^2$$

The usual volume of injectate for extradural narcotics has been 10 ml, given at L2/3. This spreads 6–8 vertebral segments, that is, it covers an area of 46.6–62.1 cm$^2$. In all the calculations $A$ has therefore been assigned a value of 50 cm$^2$.

Volume of distribution of extradural drug, $V_{ex}$

No value can be assigned to this parameter to represent the clinical situation. However, it is instructive if $V_{ex}$ is given the volume of injectate—10 ml. This model of the clinical administration then corresponds to the experimental design used for the earlier in vitro determination of dural permeabilities.

The fraction of extradural dose transferred directly across the dura, calculated using equation (2) and the above values, is shown in table IV.

These calculations indicate:

(a) the possibility of a wide range of efficiency of dural transfer, depending on the drug used,

(b) the potential for surprisingly high efficiencies of dural transfer, and

(c) the deleterious effect of increase in drug MW and lipophilicity on dural transfer.

Of the assumptions used in these calculations, the least valid is that for $V_{ex}$. This factor now becomes central to realistic estimates of dural transfer.

The nature of $V_{ex}$. In this model, $V_{ex}$ represents that volume where extradural drug is distributed,

| TABLE IV. Comparison of calculated dural transfer for morphine and buprenorphine (range). |
|-------------------------------|-------------------|-------------------|
| Molecular weight               | 285               | 467               |
| Lipophilicity*                 | -5.0              | 1.78              |
| Permeability†                  | 0.0036            | 0.00043           |
| Half-life of absorption        | 7.7 (3.1–11.5)    | 0.55 (0.1–1.0)    |
| Absorption rate constant‡      | 0.224–0.060       | 6.93–0.693        |
| % of extradural dose Transferred across dura§ | 20.0 (8.1–30.0) | 0.17 (0.03–0.3) |

The values used are those measured on a sample of human lumbar dura in vitro, as described earlier.
such that it is effectively available for transfer across the dura.

Consider the calculations in table IV. The value assigned to $V_a$ was that of the volume of injectate. This is the analogy of the in vitro situation, where the drug solution is well-stirred and where none of the drug is bound. All of the remaining drug is available all of the time to the dural surface, $A$.

Now consider the real situation after extradural drug administration in vivo:

(i) The volume into which the drug disperses is certainly not well-stirred. Dural transfer, blood removal and fat uptake will produce local concentration gradients within the volume.

Consider the case of morphine. Its low lipophilicity will give relatively low rates of blood removal and fat uptake; its low MW gives a relatively rapid dural transfer. A zone of drug depletion will occur around the immediate vicinity of the dura. Although drug can diffuse in to replenish this zone, diffusion is a slow process. By comparison with the well-stirred equivalent, this appears as a reduction in peridural drug concentration, that is an increase in $V_a$ relative to the injectate volume. Furthermore, drug which is deposited well away from the dura, such as in the paravertebral space, may not regain access to the dura. It represents an absolute loss of drug dose, which in the model appears as an increase in $V_a$ relative to the injectate volume. A highly lipophilic drug, especially if of high MW, results in an even worse situation. Rapid vascular removal and fat uptake relative to dural transfer may establish concentration gradients away from the dura. In addition, reversible binding to tissues is more pronounced with lipophilic drugs (Hollt and Teschemacher, 1975). Such binding to intervening tissues will slow diffusion, in a fashion analogous to the increase in retention time of lipophilic materials in reverse-phase partition chromatography.

These phenomena, then, are expected to increase substantially $V_a$ relative to the injectate volume. The increase should be relatively greater for the lipophilic high-MW drugs than for their less lipophilic low-MW counterparts.

(ii) Drug will become bound non-specifically to extradural tissues, reducing the free concentration. This will appear again as an increase in $V_a$ in the model. The same mechanism should also increase $k_{2a}$, as discussed previously. There will then be much less overall effect on the efficiency of dural transfer. Non-specific binding of narcotics increases as a function of lipophilicity (Hollt and Teschemacher, 1975).

The effect of the increase in $V_a$ will be to decrease proportionally the efficiency of direct dural transfer.

In the next section, the assumptions of the model are examined as a prelude to the discussion.

VALIDITY OF THE ASSUMPTIONS OF THE MODEL

Each assumption will be examined in turn:

(i) Uniformity and thickness of the dura

The dura is not uniformly thick. There is a systematic increase in dural thickness in the cephalad direction: thoracic dura is almost twice as thick as lumbar dura (Cheng, 1963). The permeability, $P$, is inversely proportional to dural thickness. Values for lumbar dura will be overestimates for more rostral dura. Within a given region there are localized areas of dural thinning, such as where nerve roots pierce the dura, and these areas will tend to increase the overall dural permeability.

Comparison of drugs using permeabilities determined on single pieces of dura will still remain valid.

(ii) Zero intradural drug concentration

The effect of this assumption may be allowed for easily with a more complicated model. Negligible differences in the extent of dural transfer result, justifying this simplifying assumption.

(iii) Extradural dose-volume relationships

This assumption is quite valid provided that the true nature of the volume term $V_a$ is understood. It is not simply the volume of injectate, but is made to encompass drug which has been effectively lost to dural transfer.

(iv) $V_a$ not a function of time

This is unlikely to be wholly true. The processes of extradural drug distribution are complex and time dependent, and $V_a$ is itself a complicated function of these processes. Such time dependency probably leads to small differences in comparison with those attributable to variations in individual extradural anatomy and in the topology of the extradural dose.

DISCUSSION OF THE MODEL

This paper is the first of a series concerned with the principles which underlie rational use of spinal narcotics. The model, although simple, allows discussion of the factors responsible for dural transfer. It should be stressed that dural transfer is only one
aspect of the series of events culminating in analgesia and other effects. Judgement of clinical efficacy must be based on an integrated overview of the end results. All of the drugs available at present were selected deliberately for parenteral use. The principles established with these narcotics may eventually provide a basis for the development and selection of opiates designed specifically for spinal use. The theory may also indicate the measurements which are worthwhile in order to establish such principles.

For dural transmission this paper suggests:
(1) The volume in which a given dose of drug is administered will, within reason, not be critical.
(2) The less lipophilic small molecular weight drugs such as morphine or pethidine will have the most efficient dural transfer.
(3) Under the best circumstances, the efficiency of dural transfer could be surprisingly high.
(4) It is likely to be the situation-dependent factors which are the cause of variations in dural transfer, leading to variation in clinical effect and even complete failure. Large differences exist between drugs, such as between morphine and buprenorphine (table I). These may subsequently be reduced substantially by differences in c.n.s. penetration and receptor affinity. This will be considered in later papers.
(5) The determination of the absorption rate constant from plasma opiate concentrations after extradural administration could provide a suitable measure of rate processes which compete with dural transmission. Early and frequent samples are required, together with an i.v. dose–decay curve.

Narcotic in sites without access to the dura will contribute to the derived absorption rate constant. The contribution of such narcotic to the plasma concentration will not be reflected in additional c.s.f. opiate concentrations in excess of those produced from blood.

(6) The \textit{in vitro} measurement of dural permeability to narcotics is simple. It would be worthwhile to extend these studies to a wide variety of narcotics, especially as anomalously high values occur (e.g. fentanyl).

Later papers will go on to consider the pharmacokinetic results of the dural transfers estimated here. This will allow comparison with clinical data, and show the typical increase in $V_e$ to more than the volume of injectate.

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REFERENCES
PERMEABILIDAD DURAL A LOS NARCOTICOS: DETERMINACION IN VITRO Y APLICACION A LA ADMINISTRACION EXTRADURAL

SUMARIO
Se midió in vitro la permeabilidad de la duramadre craneal y lumbar a diversas sustancias, incluyendo un cierto número de narcóticos analgésicos. Se presenta también información preliminar sobre materiales humanos post-mortem. La permeabilidad presenta una relación lineal con la inversa de la raíz cuadrada del peso molecular. Esas son las relaciones previstas para un proceso de difusión que está en función del peso molecular. Se calcularon los coeficientes de selectividad de masa diferencial correspondientes a la duramadre craneal y lumbar; estos fueron similares a 0,8-0,9. Dichos coeficientes fueron superiores a los de difusión en líquidos sencillos pero muy inferiores a los de membranas lípidos biológicos. Esto sugiere que las bajas tasas de difusión son una propiedad del grosor de la duramadre en vez de una impermeabilidad inherente. Se describe un modelo sencillo para la transferencia de drogas en la duramadre y su aplicación a los narcóticos. Su finalidad fue la de sugerir: los factores existentes en la transferencia de drogas en la duramadre; las propiedades físicas químicas de las drogas; la difusión, el transporte por parte de la duramadre; mediciones relevantes a futuros estudios. El modelo indica que el peso molecular de la droga y la tasa de absorción son importantes determinantes de la eficiencia de la transferencia dural. Pesos moleculares bajos y una baja absorción producen altos niveles de transferencia dural. Estos factores podrían producir una diferencia de hasta un orden de magnitud en la cantidad transferida directamente a través de la duramadre, cuando se aplican a narcóticos.

Lipidmembranen. Dies legt die Vermutung nahe, daß die niedrigen Diffusionsraten mehr eine Eigenart der Dicke der Dura darstellen als eine inhärente Undurchlässigkeit. Es wird ein einfaches Modell für den Transport von Pharmaka durch die Dura beschrieben und auf Narkosemittel angewendet. Der Sinn davon ist, die Faktoren, die eine Rolle beim Transport durch die Dura spielen und, die physiochemischen Eigenarten von Pharmaka in Beziehung zu ihrem Transport durch die Dura zu beschreiben; weltweite Bestimmungen in zukünftigen Studien vorzuschlagen. Das Modell zeigt, daß das Molekulargewicht und die Absorptionsrate wichtige Determinanten der Wirksamkeit des Transportes durch die Dura darstellen. Niedriger Molekulargewicht und langsane Absorption ergeben hohe Transportraten durch die Dura. In der Anwendung auf Narkosemittel könnten diese Faktoren von einer Unterscheidung bis sogar zu einer Größenordnung der Menge führen, die direkt durch die Dura transportiert wird.