ANALGESIC AND RESPIRATORY EFFECTS OF EXTRADURAL SUFENTANIL IN VOLUNTEERS AND THE INFLUENCE OF ADRENALINE AS AN ADJUVANT

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Intraspinal narcotics were introduced in the hope that powerful segmental analgesia could be achieved at the level of the spinal cord, without depression of the respiratory neurones in the medulla and pons (Yaksh and Rudy, 1976). Subsequent work in animals and man has shown that rostral spread in the cerebrospinal fluid (CSF) is an inescapable element of the pharmacokinetics of extradural and subarachnoid narcotics. Poorly lipid-soluble agents such as morphine, spread widely in the CSF and then gradually penetrate the surface of the neuraxis with which they come in contact. Thus morphine shows a characteristically slow onset of analgesia and a tendency to cause dangerous respiratory depression many hours after administration (Bromage et al., 1982; Camporesi et al., 1983).

In contrast, a narcotic such as sufentanil, which is approximately 1000 times more lipid-soluble than morphine, might be expected to show very different pharmacokinetics, and more favourable pharmacodynamics, based on a very rapid passage from CSF to cord lipids, with a proportionally lesser degree of rostral spread in the CSF (Cousins and Mather, 1984). Sufentanil is considered to be seven to 10 times more potent than fentanyl when given i.v. (Niemegeers et al., 1976) and so, in man, extradural doses of 10–20 μg might be expected to give results equivalent to those of extradural fentanyl in the dose range 70–100 μg. However, Donadoni and colleagues (1985) reported that 25 μg of extradural sufentanil failed to provide satisfactory clinical analgesia, although 50 μg was followed by good pain relief for 5–6 h without apparent respiratory depression.

The present study of extradural sufentanil in healthy volunteers was designed to answer four questions:

1. Is effective analgesia produced by an extradural dose of sufentanil 50 μg?
2. Are any appreciable respiratory or other side effects associated with such a dose?
3. Is the analgesia segmental in distribution?
4. Does adrenaline 1:200000, as an adjuvant, have an appreciable effect on either analgesia or any unwanted side effects?
SUBJECTS AND METHODS

Ten healthy, male volunteers between the ages of 23 and 35 yr were studied in sessions lasting 10–12 h, after written consent and institutional approval. Subjects fasted for 12 h and reclined comfortably in a 20° head-up position. A 16-gauge cannula was inserted to a suitable vein to permit fluid administration and blood sampling. Following a series of control measurements, an extradural catheter was inserted at the 2nd or 3rd lumbar space and correct catheter placement was validated by a preliminary dose of 2% chloroprocaine 10 ml. Thirty minutes after complete regression of the chloroprocaine block, sufentanil 50 μg, made up to a volume of 10 ml with normal saline, was injected through the extradural catheter, and the catheter and attached micropore filter (0.2-μm pore-size) were flushed with 1.5 ml of saline. Plain sufentanil was injected at the first session. Eight of the 10 subjects returned for a second session 2–3 months later, when adrenaline 1:200 000 (5 μg ml⁻¹) was added to the same dose and volume of sufentanil. All subjects attended a pre-trial session on the day before the first test session, in order to familiarize themselves with the tests and the apparatus, and to lessen any chances of experimental error arising from anxiety or misunderstanding.

The following tests were performed in a resting control period, and then at intervals for 6–8 h after the extradural injection of sufentanil.

Blood sampling
Venous blood samples were drawn from a large forearm vein at 2, 5, 10, 20, 30 and 60 min, and then hourly for 6 h. Ten millilitre of blood was drawn into heparinized syringes and centrifuged at 1100 rev min⁻¹ for 10 min. The supernatant plasma was analysed (for sufentanil concentration) by radioimmunoassay. The assay has a lower limit of detection of 0.1 ng ml⁻¹ and an accuracy of ±12%.

Algesimetry
Periosteal pressure was applied over forehead, sternum and the anterior surface of the tibia using a calibrated, spring-loaded steel rod of 32 mm² cross-sectional area (Bromage, Camporesi and Leslie, 1980). Increasing pressure was applied steadily over each measurement area at the rate of 0.5 kg s⁻¹ and the subjects were instructed to say “stop” as soon as the pressure became painful. Three consecutive readings were taken at each site and the average recorded. A fresh adjacent pressure site was taken for successive readings, to minimize tissue bruising and resultant changes in sensitivity.

The Cold Pressor Response Test (CPRT) was measured in hand and foot as described previously (Bromage, Camporesi and Leslie, 1980). The extremity was immersed in ice-water for 2 min while arterial pressure was measured every 30 s by cuff and auscultation in the opposite arm. The pressor response was taken to be the arithmetic mean of the systolic and diastolic arterial pressures measured at 60, 90 and 120 s of immersion, and expressed as a percentage change from the pre-immersion mean. The limb was then rewarmed on a heating blanket and between tests the arterial pressure was allowed to subside to control baseline readings. Cold pressor responses in hand and foot were measured before extradural injection, at 30 min, 60 min and then hourly for 7 h after the extradural administration of sufentanil. Subjects were instructed to record the degree of pain experienced by ice-water immersion on a linear analogue scale of 0–10 cm, where 0 was no pain and 10 the worst imaginable.

Respiratory sensitivity to carbon dioxide
Respiratory depression was assessed by measurements of end-tidal carbon dioxide partial pressure, and by carbon dioxide response curves using a modification of Read's rebreathing method (Camporesi et al., 1983). Subjects breathed through a mouthpiece and nose-clip system into a 9-litre reservoir charged with 5 % carbon dioxide in oxygen, until the partial pressure of expired carbon dioxide reached 7.33 kPa. Expired gas was extracted at the mouthpiece at the rate of 200 ml min⁻¹ and returned to the reservoir system. Expired carbon dioxide and ventilatory volume were measured on a breath-by-breath basis, using a Beckman infra-red carbon dioxide analyser and a Fleisch pneumotachograph integrated for volume. The volume of each breath and partial pressure of end-expired carbon dioxide were displayed on an Apple II microcomputer screen, stored on floppy discs and printed out at the end of each rebreathing run, together with the equation for the line of the carbon dioxide response curve, calculated by the sum of least squares, and the $V_{E_{50}}$ (minute ventilation when end-expired carbon dioxide = 50 mm Hg) (Sherrell and Swanson, 1986).
Four control carbon dioxide response curves were measured before extradural injection and then at 10 min, 45 min, 90 min and thereafter hourly for 6.5 h after administration of the sufentanil. Dermatome levels of hypalgesia to ice and pin scratch were measured at frequent intervals after the extradural injection of sufentanil. Side effects of pruritus, somnolence, nausea and vomiting were also noted.

Statistical analysis

All results were expressed as percentage changes from control. To take advantage of the paired data structure, statistical comparisons between sufentanil, and sufentanil plus adrenaline, were made excluding the two subjects who did not return for the adrenaline session. The statistical procedure used is based on a randomization analysis of randomized block design that has been extended to growth and response curves (Zerbe, 1979a). This is a non-parametric test that permits comparison of several pre-specified time intervals chosen by the investigators. To test for significant differences at these intervals, we used the approximate P values as determined by the standard F distribution with the degrees of freedom as suggested by Zerbe (1979b).

Non-respiratory side effects such as pruritus, nausea, vomiting, somnolence and urinary retention were compared using the chi-squared test.

An estimate or risk:benefit ratio following extradural narcotics may be made by setting arbitrary limits for clinically useful analgesia and for acceptable respiratory risk. Cartwright and his colleagues (1983) found that 50% reduction of the carbon dioxide response curve was associated with a $P_{A}CO_{2}$ of 45 mm Hg, which they chose to represent the border of critical respiratory depression, and for the purpose of this study we have selected the same arbitrary index of impending respiratory depression. The arbitrary lower limit of analgesic efficacy has been estimated at 50% depression of CPRT, since earlier studies with extradural morphine indicated this to be approximately equivalent to adequate analgesia for relief of postoperative lower abdominal pain, while 75% depression of CPRT was equivalent to adequate analgesia for upper abdominal pain. Individual post-drug data points for depression of the carbon dioxide response slope were plotted against this arbitrary grid of 50% depression of CPRT and 50% depression of carbon dioxide response, to obtain 2 × 2 tables of four risk–benefit groups: 1 = safe; 2 = unsafe; 3 = effective; 4 = ineffective. The Mantel and Haenzel chi-square test was applied to these data to distinguish the effects of sufentanil from those of sufentanil with adrenaline.

RESULTS

Blood concentrations of sufentanil

Circulating sufentanil was detected in only five of the 10 subjects receiving the plain solution and in four of the eight subjects receiving the adrenaline-containing solution. Average blood concentrations were low and evanescent (table I). The plain solution showed a peak at 2 min, but no drug was detectable after 30 min. The adrenaline solution peaked at 5 min and traces persisted until 120 min. However, these differences were not statistically significant at any time.

Segmental hypalgesia

Segmental hypalgesia to ice and pin-prick developed rapidly—within 15 min of the injection of sufentanil, but appeared sooner after sufentanil with adrenaline (three subjects within 5 min) and extended to between T11 and T9. Upper levels

<table>
<thead>
<tr>
<th>Table I. Average concentrations of sufentanil in venous blood (ng ml⁻¹) after lumbar extradural injection of sufentanil 50 μg plain or with adrenaline 1:200 000 (means ± SD). nd = Not detectable; ns = no significant difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (min)</td>
</tr>
<tr>
<td>Plain sufentanil (n = 10)</td>
</tr>
<tr>
<td>(±2.78)</td>
</tr>
<tr>
<td>Sufentanil + adrenaline (n = 8)</td>
</tr>
<tr>
<td>(±0.08)</td>
</tr>
<tr>
<td>ns</td>
</tr>
</tbody>
</table>
of sensory modulation extended to T9 ± 1 with sufentanil plus adrenaline and to T10 ± 1 with the plain solution. The upper level of hypalgesia remained constant for each subject and did not spread rostrally with either plain sufentanil or sufentanil with adrenaline.

Subjective analgesia

Linear analogue estimate of CPRT pain. All subjects complained of moderate to severe pain during ice-water immersion of an extremity. The average control scores on the linear analogue scale of 0 (no pain) to 10 (most severe pain imaginable) were 6.9 ± 0.31 cm for the hand, and 7.1 ± 0.29 cm for the foot. Profound subjective analgesia occurred in the foot, with a 70–90% depression lasting 1.25 h after plain sufentanil and 2 h after sufentanil with adrenaline (fig. 1). Sufentanil with adrenaline caused very little relief in the hand, but plain sufentanil produced a 50% reduction of linear analogue score for about 1.5 h, probably reflecting a greater degree of vascular uptake and systemic analgesia when adrenaline was omitted.

Periosteal pressure. The average control tolerances for periosteal pressure were 97.8 ± 8.9 g mm⁻² for forehead, 98.4 ± 8.0 g mm⁻² for sternum and 138.1 ± 8.8 g mm⁻² for tibia. Tolerance to periosteal press pressure was increased most in the leg and least in the forehead (fig. 2A, B).

The forehead showed a very slight increase in tolerance in the range 10–20% for 3 h after plain sufentanil and 10–30% after sufentanil with adrenaline. Analgesia in the tibia was most intense during the first 1.5 h, with increased tolerance ranging from 40 to 50% for plain sufentanil and 55 to 85% for sufentanil with adrenaline.

Cold Pressor Response Test. The mean control hypertensive response to ice-water immersion of the hand was 36.8 ± 2.03 (SEM)% above resting arterial pressure and 33.9 ± 1.73% above resting values for the foot. Depression of cold pressor response after extradural sufentanil with adrenaline was greater in the foot than in the hand, and greatest when sufentanil with adrenaline was administered (fig. 3). It can be seen that the curves for foot and hand are more widely separated when sufentanil with adrenaline was given (P = 0.0006) than with sufentanil alone (P = 0.014), and a profound depression of CPRT in the foot to 70–85% below control persisted for 5 h after sufentanil with adrenaline.

Ventilation

In Denver, at an altitude of 1603 m and a barometric pressure of 84.0 kPa, PE'CO₂ is set lower than at sea level; in this series the average resting control value was 4.41 ± 0.09 kPa. End-tidal Pco₂ increased rapidly and significantly to about 15% above control during the first 2 h after plain sufentanil and then declined to 8.5% above control by the 7th hour. On the other hand, sufentanil with adrenaline was followed by a

• = Forehead; △ = sternum; ▲ = tibia.

FIG. 3. Percentage reduction of cold pressor response in hand and foot after extradural sufentanil 50 μg (means ± SEM). Plain sufentanil: □ = hand, ○ = foot; sufentanil + adrenaline: ■ = hand, ● = foot.
FIG. 4. Percentage change of resting $P_E\text{CO}_2$ after extradural sufentanil 50 µg (means ± SEM). O = Plain sufentanil; ● = sufentanil + adrenaline.

FIG. 5. Percentage change of slope of carbon dioxide response curve ($\Delta V_E/\Delta P_E\text{CO}_2$) after extradural sufentanil 50 µg (means ± SEM). O = Plain sufentanil; ● = sufentanil + adrenaline.

FIG. 6. Percentage change of $V_{E}\text{so}_2$ after extradural sufentanil 50 µg (means ± SEM). O = Plain sufentanil; ● = sufentanil + adrenaline.
gradual increase to a peak of 14% above control by 4.5 h, which then declined to 8% above control by the 7th hour (fig. 4). Responses to acute carbon dioxide challenge showed a similar temporal pattern (figs 5, 6). Depression of the slope of the carbon dioxide response curve by 47.5% and of $V_{E_{50}}$ by 56% was abrupt and marked with plain sufentanil, whereas sufentanil with adrenaline induced a more gradual depression of the slope to −36% by the 4th hour and a reduction of $V_{E_{50}}$ to −53% in the 5th hour, followed by a gradual but incomplete recovery by the 7th hour (fig. 6). A few apnoeic periods of longer than 10 s were observed, but none exceeded 30 s.

**Non-respiratory side effects**

Non-respiratory side effects developed almost as rapidly as segmental analgesia and were evident within 30 min of the administration of the sufentanil, except in one subject who developed mild and probably unrelated headache for 4 h after sufentanil plus adrenaline. Incidence, intensity and duration of side effects tended to be greater with plain sufentanil than with sufentanil plus adrenaline, and this difference was most marked in the case of drowsiness (table II). This ameliorating effect of adrenaline on non-respiratory side effects was unexpected, since it was in direct contrast to our earlier studies with extradural morphine, where all side effects were made worse by adding adrenaline (Bromage et al., 1983). No arterial hypotension occurred and dizziness and light-headedness were not accompanied by any cardiovascular instability.

**Risk: benefit ratio**

Seven post-drug measurements of CPRT and carbon dioxide response were obtained in eight subjects at each of the two study sessions, yielding a total of 112 data points for percentage depression of CPRT and percentage depression of carbon dioxide response slope. Table III shows the distribution of these points in terms of greater or less than 50% depression of either index. The

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**Table II. Incidence, intensity and duration of non-respiratory side-effects after extradural sufentanil 50 μg with and without adrenaline. *P < 0.05 (Fisher's exact test); NA = not applicable**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Incidence</th>
<th>Average intensity scale (1–3)</th>
<th>Average duration (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>7/10</td>
<td>0.9</td>
<td>4.0</td>
</tr>
<tr>
<td>Nausea</td>
<td>2/10</td>
<td>0.35</td>
<td>2.75</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2/10</td>
<td>0.2</td>
<td>0.25</td>
</tr>
<tr>
<td>Headache</td>
<td>1/10</td>
<td>0.2</td>
<td>7.0</td>
</tr>
<tr>
<td>Light headedness</td>
<td>7/10</td>
<td>1.05</td>
<td>1.6</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>7/10*</td>
<td>1.1</td>
<td>4.0</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>3/10</td>
<td>NA</td>
<td>5.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Incidence</th>
<th>Average intensity scale (1–3)</th>
<th>Average duration (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>7/8</td>
<td>1.2</td>
<td>1.7</td>
</tr>
<tr>
<td>Nausea</td>
<td>1/8</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1/8</td>
<td>0.125</td>
<td>0.05</td>
</tr>
<tr>
<td>Headache</td>
<td>2/8</td>
<td>0.3</td>
<td>5.0</td>
</tr>
<tr>
<td>Light headedness</td>
<td>1/8</td>
<td>0.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>0*</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>1/8</td>
<td>NA</td>
<td>6.0</td>
</tr>
</tbody>
</table>

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**Table III. Comparative safety and efficacy of plain sufentanil and sufentanil with adrenaline 1 : 200000, from 112 observations of CPRT and carbon dioxide response in eight subjects. Safety: Sufentanil with adrenaline superior to sufentanil ($\chi^2 = 5.714, P < 0.025$). Efficacy: Sufentanil with adrenaline superior to sufentanil ($\chi^2 = 4.057, P < 0.05$)**

<table>
<thead>
<tr>
<th>Safety</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&lt; 50% depression of $\Delta \dot{V}<em>{E}$/Δ$P</em>{E_{CO_2}}$)</td>
<td>(&gt; 50% depression of CPRT)</td>
</tr>
<tr>
<td>Safe</td>
<td>Unsafe</td>
</tr>
<tr>
<td>Plain sufentanil</td>
<td>39</td>
</tr>
<tr>
<td>Sufentanil + adrenaline</td>
<td>50</td>
</tr>
</tbody>
</table>
distribution indicates that adrenaline reduced risk significantly \((P < 0.025)\) while conferring a significant improvement in efficacy \((P < 0.05)\).

**DISCUSSION**

Laboratory investigations of analgesic efficacy and safety may be criticized as irrelevant to clinical management but, on the contrary, they provide insight to questions which could not be answered in any other way, and they fill a void left by the inadequacies in the design of postoperative investigations. Postoperative patients make poor subjects. They are fatigued and in pain, and they cannot be relied upon to co-operate effectively and consistently, for many hours on end, in physically demanding studies. One analysis of postoperative hypercapnic responses concluded that approximately one-half of all such estimates may have to be excluded as unreliable (Goodman and Black, 1985). In another study of pain and postoperative analgesia one of us (P.R.B.) found that two out of three pulmonary pressure–volume estimations were technically unacceptable, and the investigation was abandoned.

On the other hand, healthy volunteers are sturdy, articulate subjects with the stamina to provide consistent responses throughout a long and gruelling programme. While laboratory algesimetry cannot mirror surgical pain precisely, it serves as an acceptable approximation and provides a proving ground to study the effects of altering one variable at a time, and to guide appropriate designs for subsequent clinical trials.

In this study, greatest emphasis has been placed on two objective tests, the cold pressor response and measurements of central respiratory drive. The cold pressor response test simultaneously performs tasks of both generating pain and measuring the response in an objective and consistently repeatable manner that is free of acute tolerance, conscious control or decision making (Hines and Brown, 1933; Godden, Roth and Hines, 1955). Although carbon dioxide responses vary widely between individuals, and even from day to day, measurements in males on any given day are highly repeatable, with a coefficient of variation of about 15\% (Sahn et al., 1977; Scamman and Ghoneim, 1983).

Two subjective tests, periosteal pressure and the linear analogue scale, were included as supportive data. The linear analogue scale plays the additional and important role of documenting a simple, unsophisticated link between this study and others, where the linear analogue was used in an attempt to quantitate laboratory or clinical pain and analgesia. Thus, our control score of 7.1 with a reduction of 73\%, 1 h after the administration of plain sufentanil, compares fairly closely with the results of Donadoni and colleagues (1985), who found a reduction of 96\% after a similar control score and extradural dose of sufentanil following orthopaedic surgery on the lower limb.

Our algesimetric tests showed that sufentanil in 50-\mu g doses produced very rapid and effective analgesia of a strongly segmental nature. Limitation of segmental spread was not perfect, since an appreciable degree of analgesia was observed in the sternum and upper limb, reflecting some degree of rostral spread to the thoraco–cervical region. However, the forehead was virtually unaffected, while the upper level of cutaneous hypalgesia to pin–prick remained steadfastly fixed in the lower thoracic segments until analgesia waned. This constancy of dermatome hypalgesia was in marked contrast to earlier findings with extradural morphine, when cutaneous hypalgesia spread slowly upwards to reach trigeminal territory by the 5th–8th hours, and when adrenaline hastened and intensified this upward spread (Bromage et al., 1982, 1983).

Both subjective and objective evidence of analgesia in figures 1, 2 and 3 show that segmental hypalgesia was more sharply defined after sufentanil with adrenaline than after plain sufentanil. The separation of quality of analgesia in hand and foot, and its exaggeration by adrenaline, is seen most clearly in the linear analogue scores in figure 1. These curves may reflect a more rapid and extensive vascular uptake and systemic effect with plain sufentanil as well as a more complete uptake in the lower spinal cord with sufentanil and adrenaline. However, blood concentrations were too low and too evanescent to support any conclusions about the influence of vascular uptake. Cord uptake is likely to be the more important of these two variables, since strong subjective analgesia in the foot persisted into the 6th hour with the adrenaline solution, and far beyond the time when circulating sufentanil had become undetectable. How can these algesimetric results be translated from laboratory-induced pain to the real intensity of clinical pain? Earlier work with extradural narcotics in patients and volunteers suggests that doses sufficient to produce a 70–75\% depression of CPRT provide strong
analgesia, equivalent to that required to alleviate severe postoperative pain associated with upper abdominal or thoracic surgery. A 50% depression of CPRT is roughly equivalent to the degree of analgesia required for less severe pain associated with lower abdominal procedures (Bromage, Camporesi and Chestnut, 1980; Bromage, Camporesi and Leslie, 1980; Bromage et al., 1983).

If such an equivalent scale is applied to figures 1 and 3, it can be estimated that plain extradural sufentanil in a 50-μg dose will provide about 1.5 h of adequate analgesia for upper abdominal pain and about 3.5 h of satisfactory pain relief from lower abdominal pain. The adrenaline-containing solution will give a similar degree of relief for 4.5 h after upper abdominal surgery and for 5.5 h after lower abdominal operations. These estimates of duration of clinical analgesia may be conservative, for they fall short of the figure of 5–6 h reported by Donadoni and colleagues (1985) after 50 μg of the plain solution following lower limb surgery.

The non-respiratory effects of pruritus, nausea, retention of urine and depressed mentation were of trivial severity and incidence when compared with extradural morphine 10 mg in volunteers, and unlike morphine or fentanyl, these unwelcome side effects were diminished rather than worsened by the addition of adrenaline (Bromage et al., 1983; Welchew, 1983; Robertson, Douglas and McMorland, 1985).

Unfortunately, as in all other volunteer studies in which respiratory control has been measured, respiratory depression accompanied analgesia. However, the effects of adrenaline as an adjuvant to extradural sufentanil were markedly different from its action with extradural morphine in volunteers, in whom adrenaline caused a proportionate increase in both analgesia and undesirable side effects, including alarmingly long apnoeic intervals lasting from 15 to 50 s (Bromage et al., 1983; Camporesi et al., 1983). In the present series, adrenaline intensified and prolonged segmental analgesia without causing a corresponding increase in respiratory depression.

In summary, our results show that extradural sufentanil 50 μg provides effective analgesia of 2–3 h duration, and that intensity of analgesia is enhanced and duration prolonged to 4.5–5.5 h by the addition of adrenaline 5 μg ml⁻¹. Both non-respiratory and respiratory side effects are less when adrenaline is added to sufentanil. This favourable performance of sufentanil with adrenaline, in volunteers, suggests that the combination is suitable for wider evaluation under conditions of clinical trial.

ACKNOWLEDGEMENTS
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REFERENCES

