PROSTAGLANDIN-SYNTHETASE INHIBITION WITH DICLOFENAC SODIUM IN TREATMENT OF RENAL COLIC: COMPARISON WITH USE OF A NARCOTIC ANALGESIC

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Summary

Ureteric obstruction causes increased synthesis and release of prostaglandins. As a result renal pelvic pressure rises, causing renal colic. This double-blind study in 66 patients with acute renal colic shows that intramuscular injection of a potent prostaglandin-synthetase inhibitor (diclofenac sodium) is more effective and has fewer side-effects than a narcotic drug commonly used to treat ureteric colic.

Introduction

Ureteric colic is usually treated with narcotic analgesics, often combined with a spasmolytic agent. Side-effects and the risk of drug addiction indicate the need for an alternative to narcotics. Prostaglandin-synthetase inhibition by intramuscular injection of diclofenac sodium, a potent prostaglandin-synthetase inhibitor, has been shown to relieve renal colic more effectively than placebo. In that study complete relief of pain was achieved in 70% of the patients after one injection of 50 mg diclofenac sodium and in 90% after another injection. This striking effect may be explained by reduction of the rise in intrapelvic pressure mediated by release of prostaglandins in the kidney during ureteric obstruction. This new treatment has so far not been compared to conventional treatment in a controlled double-blind trial. This study compares the effectiveness of diclofenac sodium with that of a narcotic analgesic combined with a spasmolytic drug.

Patients and Methods

Patients with attacks of ureteric colic admitted to the emergency wards of our hospitals were studied. All were examined by a surgeon, and their symptoms, blood pressure, pulse rate, and results of urine analysis were recorded. Patients who fulfilled clinical criteria of ureteric colic were randomly allocated to treatment with intramuscular injection of either 50 mg 'Voltaren' ('Voltarol', diclofenac sodium) or 1 ml 'Spasmofen' (containing methylscopolamine nitrate 0·15 mg, papaverine chloride 20 mg, noscapine hydrochloride 6·6 mg, codeine chloride 0·4 mg). Spasmofen was chosen for comparison, since it is one of the preparations most widely used in Sweden for ureteric colic. The dose of 1 ml, the contents of one ampoule, is considered safe in adults irrespective of body mass or age.

Before the injection the patients' pain was recorded by the surgeon as either "moderate" or "severe". The analgesic effect 30 min after the injection was assessed by the patient as: "no effect", "partial relief", or "complete relief" of pain. At that time, blood pressure, pulse rate, and side-effects were recorded. The patients were specifically asked if they experienced drowsiness, nausea, dizziness, or other side-effects.

The protocol had been passed by the ethical committee of the Medical Faculty of Göteborg, and informed consent was given by all patients. All patients were followed up in the clinic. If the diagnosis of renal colic was not confirmed by urine analysis, intravenous urography, or voiding of a calculus, the patient was excluded.

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Statistics

Differences between means were studied with Student's t-test. Differences in frequencies between groups were analysed with Fisher's exact probability test. Significance levels of p<0·05 were accepted (two-tailed).

Results

34 patients treated with voltaren were compared with 32 patients treated with spasmofen. There were no significant differences between the two groups in sex, age, or pretreatment pain (table I).

Partial or complete relief of pain within 30 min of the injection was achieved in 31 of the 34 patients treated with voltaren compared with 20 of 32 treated with spasmofen (p=0·02).

The most common side-effect was drowsiness (10 patients on voltaren, 8 on spasmofen). Nausea was registered in 3 patients in each group. Dizziness was registered in 1 patient receiving voltaren and in 4 receiving spasmofen. 2 patients in the spasmofen group experienced other side-effects (dry mouth) compared with none in the voltaren group.

A slight but statistically significant fall in systolic blood pressure was found in the voltaren group. No statistically significant changes in pulse rate or blood pressure were registered in the spasmofen group (table II).

Discussion

This study shows that intramuscular injection of a compound that inhibits prostaglandin synthesis is remarkably effective in treating attacks of renal colic. Renal colic is caused by tension in the wall of the renal pelvis due to a rise in pressure above the ureteric obstruction. This elevation of pressure in the renal pelvis stimulates prostaglandin synthesis, which increases diuresis, causing a further rise in pressure. The rationale for using prostaglandin-synthetase inhibitors in the treatment of renal colic is thus to counteract the increased synthesis and release of prostaglandins, which are of pathogenetic importance in this condition.

The side-effects were less common with voltaren (diclofenac sodium) than with spasmofen. Drowsiness and nausea were equally prevalent with the two treatments. Conceivably the long duration of pain, often with disturbed sleep, could explain the drowsiness, and nausea is common in

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**TABLE I—SEX, AGE, AND ASSESSMENT OF PAIN BEFORE TREATMENT WITH VOLTAREN OR SPASMOFEN**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Voltaren (n=34)</th>
<th>Spasmofen (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Female</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>17-69</td>
<td>22-84</td>
</tr>
<tr>
<td>Moderate pain</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Severe pain</td>
<td>19</td>
<td>18</td>
</tr>
</tbody>
</table>

**TABLE II—BLOOD PRESSURE AND PULSE RATE BEFORE AND 30 MIN AFTER TREATMENT WITH VOLTAREN OR SPASMOFEN (MEAN±SE)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Voltaren</th>
<th>Spasmofen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>140±3</td>
<td>134±3</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>87±2</td>
<td>84±2</td>
</tr>
<tr>
<td>Pulse rate/min</td>
<td>70±2</td>
<td>70±3</td>
</tr>
</tbody>
</table>

**Discussion**

This study shows that intramuscular injection of a compound that inhibits prostaglandin synthesis is remarkably effective in treating attacks of renal colic. Renal colic is caused by tension in the wall of the renal pelvis due to a rise in pressure above the ureteric obstruction. This elevation of pressure in the renal pelvis stimulates prostaglandin synthesis, which increases diuresis, causing a further rise in pressure. The rationale for using prostaglandin-synthetase inhibitors in the treatment of renal colic is thus to counteract the increased synthesis and release of prostaglandins, which are of pathogenetic importance in this condition.

The side-effects were less common with voltaren (diclofenac sodium) than with spasmofen. Drowsiness and nausea were equally prevalent with the two treatments. Conceivably the long duration of pain, often with disturbed sleep, could explain the drowsiness, and nausea is common in
attacks of renal colic. Thus these symptoms should not necessarily be considered side-effects of the treatment. It is likely, however, that larger doses of the narcotic would significantly increase the side-effects.

A slight fall in systolic blood pressure was recorded after treatment with diclofenac sodium as in our previous study.2 It is not known if this is a pharmacological effect or an effect of pain relief. The absence of this phenomenon in the spasmofen group might be explained by a poorer therapeutic effect, with more residual pain and/or the content of the anticholinergic agent, methylscopolamine, in that drug. Intramuscular injection of the prostaglandin-synthetase inhibitor diclofenac sodium was significantly more effective in the treatment of renal colic than was a commonly used narcotic preparation. Furthermore, diclofenac sodium seemed to have fewer side-effects. It is suggested that this treatment is an attractive alternative that might replace narcotic drugs in the routine management of this common disorder.

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REFERENCES

Preliminary Communication

SUSTAINED SUPPRESSION OF TESTOSTERONE PRODUCTION BY THE LUTEINISING-HORMONE RELEASING-HORMONE AGONIST BUSERELIN IN PATIENTS WITH ADVANCED PROSTATE CARCINOMA

A New Therapeutic Approach?

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Summary

Nine patients with advanced carcinoma of the prostate were treated with the luteinising-hormone-releasing-hormone agonist buserelin (2 mg/day subcutaneously for 3 days then 0·4–1·2 mg/day intranasally for up to 24 weeks). There was a rise in luteinising-hormone levels during the first few days of treatment, but levels fell after 3 weeks and remained lower than normal after 24 weeks' treatment. In patients receiving 0·6–1·2 mg buserelin per day testosterone levels fell to less than 1 ng/ml within 3 weeks and were still as low as those found in surgically castrated men after 24 weeks. Histology showed regressive changes in some tumours after 3–6 months' buserelin treatment similar to those seen in surgically castrated men. Buserelin treatment may be an attractive alternative to surgery in patients with advanced carcinoma of the prostate.

INTRODUCTION

PULSATILE secretion of luteinising hormone releasing hormone (LH-RH) is a prerequisite of normal gonadal function. Pituitary gonadotropin release may be pharmacologically stimulated by LH-RH agonists as well as by natural LH-RH; these agonists are 20–170 times more potent.1–5

In male animals continuous administration of high doses of LH-RH agonists can lead to loss of reproductive function.6–8 In rats the subcutaneous injection of buserelin, one of the most potent LH-RH analogues, causes reductions in testosterone levels and in ventral prostate, seminal vesicle, and testis weight.4 5 Few data have been published about any anti-fertility effect in man.9–12

This chemical approach may be relevant to treatment of testosterone-dependent diseases. We have therefore studied the long-term effect on testosterone production in patients with advanced prostatic carcinoma of buserelin given subcutaneously at first and then intranasally. With intranasal administration, the absorption rate is only 1%.1,4

PATIENTS AND METHODS

Nine patients (aged 62 to 79 years) gave informed written consent to participate in the study. All had carcinoma of the prostate, stage T4 (TNM classification), confirmed by histology and cytology. The sexual activity of all patients had ceased before they underwent treatment.

Various dose regimens of buserelin were investigated. Treatment was initiated with a dose of 2 mg/day buserelin in two doses injected subcutaneously at 6 A.M. and 8 P.M. for 3 to 6 days and was then continued with 0·4–1·2 mg/day, given in three doses at 8 A.M., 2 P.M., and 10 P.M. The treatment period ranged from 6 to 24 weeks.

Three men, aged 70, 67, and 70 years, completed the full 24-week treatment period. Blood samples were taken every 4 h from the day before treatment until the 5th treatment day, then three times a day for 3 weeks, and subsequently once a week. Luteinising-hormone (LH) and testosterone levels were measured in all samples.

Serum LH was determined by means of a coupling antisera technique with a commercially available kit (Serono, Italy); Serono LH is standardised to correspond to the first International Reference Preparation, MRC 68/40. The lowest level measurable is 0·5 mU/ml with an incubation period of 48 h.

Serum testosterone levels were measured with an anti-testosterone-3-(carboxymethylxoxime) bovine serum albumin antisera (Steranti Research Ltd., St Albans, U.K., batch no. 8802) This antisera shows 36% cross-reactivity with 5-alpha-dihydrotestosterone. Testosterone was extracted from serum with ethanol, the samples were dried down with nitrogen, and then diluted in 0·1% gelatine/phosphate-buffered saline buffer. An aliquot of each was incubated overnight with 100 µl antisera and 100 µl tritiated testosterone. Bound and free fractions were separated by the dextran-coated charcoal technique. The bound fraction was added to a scintillation cocktail and measured by a scintillation counter. The lowest measurable testosterone level by this assay is 40 pg/ml. The within-assay and between-assay variations for both hormones were less than 12%.

The normal serum testosterone level ranges from 2·5 to 10 ng/ml. The testosterone levels in a control group of twenty castrated men (aged 60 to 80 years) ranged from 0·1 to 0·8 ng/ml (mean, 0·35 ng/ml). The basal LH level in normal men is 5–25 mU/ml.