EFFECT OF PHYSOSTIGMINE ON MORPHINE-INDUCED POSTOPERATIVE PAIN AND SOMNOLENCE

M. WEINSTOCK, J. T. DAVIDSON, A. J. ROSIN AND H. SCHNIEDEN

SUMMARY

The effects of physostigmine 1 mg i.v. were studied on the analgesia, sedation and reduction in respiratory rate induced by morphine 10 mg/60 kg i.v. in 10 patients recovering from surgery. Within 5–10 min, physostigmine abolished the somnolent effect of morphine and restored the respiratory rate to pre-drug values. Analgesia, assessed by an independent observer and by the patient was, if anything, increased by physostigmine. The analeptic effect of physostigmine lasted 40–60 min.

An important factor limiting the use of morphine in acutely painful conditions is the well documented danger of significant respiratory depression. Somnolence, while less of a problem, may be a troublesome side-effect. Our previous studies in experimental animals have shown that physostigmine, an anticholinesterase agent that readily penetrates the central nervous system, can reverse the respiratory depressant effect of morphine without reducing the analgesic activity (Weinstock et al., 1980). Physostigmine was also found to antagonize the respiratory depressant effect of morphine given as part of the pre-anaesthetic medication to human subjects (Snir-Mor, Weinstock and Davidson, 1981).

These findings suggest that physostigmine may be of value in antagonizing the side-effects of morphine after surgery. However, a possible role for physostigmine in such patients would be largely vitiated if the analgesic effect of morphine was reversed.

The present study was undertaken to determine the effect of physostigmine on the somnolence induced by morphine and to clarify if it alters the level of analgesia in the postoperative period.

METHODS

The study was carried out in the postoperative ward of Hadassah University Hospital, Jerusalem, in patients recovering from abdominal surgery, who were free from cardiovascular and respiratory disease. Informed consent was obtained. Seventeen male patients were studied of whom eight underwent retropubic prostatectomy, eight inguinal herniorrhaphy and one lumbar sympathectomy. The age range was 42–81 yr (mean 64.9 ± 3.5) and the average weight, 72.1 ± 1.9 kg. Surgery had been carried out under lumbar extradural block. No narcotics or sedative drugs were administered before or during surgery other than diazepam 10 mg orally 90 min before operation. Thus, the subjects were free from postanaesthetic sedation and confusion which could have impaired our ability to assess the drug combination.

Our observations were commenced when the influence of the local extradural anaesthetic had waned and the patients were complaining of moderate to severe pain. The degree of pain was assessed by the patient by means of a pain chart according to the degree of severity listed on the left-hand side of table I. An independent observer who was unaware of the treatment being administered, recorded the

<table>
<thead>
<tr>
<th>TABLE I Grading of pain severity</th>
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<tbody>
<tr>
<td>Patient estimate</td>
</tr>
<tr>
<td>--------------------</td>
</tr>
<tr>
<td>Very severe</td>
</tr>
<tr>
<td>Severe</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Slight</td>
</tr>
<tr>
<td>None</td>
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degree of pain envinced by the patient according to a five-point scale as shown on the right-hand side of table I (modified from Dundee, 1980).

Patients were also rated for sedation by the independent observer according to the rating scale shown in table II. Measurements of heart rate, arterial pressure and respiratory rate were made at 10-min intervals throughout the study. After two initial assessments of pain and sedation and recordings, all patients were given droperidol (dehydrobenzperidol 2.5–5 mg i.v.) to prevent the possibility of vomiting caused by morphine or physostigmine, and the assessments were repeated 10 and 20 min later. Droperidol was selected in preference to phenothiazines because of its relatively low anticholinergic activity (Greene, 1972).

Because of their relatively advanced age, six patients were given morphine hydrochloride by i.v. infusion over 5 min at a dose of 5 mg/60 kg, and this was followed 25–30 min later by a further 5 mg/60 kg. The remaining 11 patients were given morphine 10 mg/60 kg i.v. over 5 min as a single dose. Thirty minutes after the 10-mg dose or the second 5-mg dose of morphine, Scobutan (N-butylhyoscine hydrobromide 5 mg) was injected i.v. to block peripheral muscarinic cholinergic receptors. Scobutan was used rather than the more familiar atropine as there is evidence that the latter may produce prolonged sedation by blocking cholinergic transmission in pathways concerned with arousal and awareness (Longo, 1966). Furthermore atropine which, unlike Scobutan, passes the blood–brain barrier (Herz et al., 1965), may be expected to antagonize the central cholinergic effects of physostigmine. In 10 of the patients (experimental group), physostigmine salicylate, 1 mg/60 kg was given 10–15 min later by i.v. infusion over 5 min. The remaining seven patients (control group) received 2 ml of saline instead of physostigmine.

Assessments of pain, sedation, respiratory and heart rates and arterial pressure were continued for up to 45 min after the administration of physostigmine.

Scored data were analysed using the Mann–Witney test for non-parametric data. Other measurements were analysed using the paired t-test.

RESULTS

The typical sequential responses obtained in all 10 patients to morphine and physostigmine are illustrated in figure 1 for patient no. 2 (prostatectomy). In all 17 patients morphine produced a significant

<table>
<thead>
<tr>
<th>Score</th>
<th>Observer estimate</th>
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<tbody>
<tr>
<td>5</td>
<td>Patient does not respond to the spoken word</td>
</tr>
<tr>
<td>4</td>
<td>Patient responds sluggishly and relapses into sleep</td>
</tr>
<tr>
<td>3</td>
<td>Patient lying with eyes closed, but responds immediately when spoken to</td>
</tr>
<tr>
<td>2</td>
<td>Patient appears normal and alert, but does not initiate conversation</td>
</tr>
<tr>
<td>1</td>
<td>Patient initiates conversation and is fully aware of surroundings</td>
</tr>
</tbody>
</table>

**FIG. 1** The effects of morphine and physostigmine given sequentially on pain, wakefulness, respiratory rate and mean arterial pressure in one patient recovering from surgery. Droperidol and Scobutan given as bolus i.v. injections at times indicated by arrows. Morphine and physostigmine given as slow i.v. infusions during time indicated by double arrows.
degree of analgesia (a reduction of two points on the pain scale) 15–30 min after a total of 10 mg/60 kg had been given. This was always accompanied by marked sedation, and small but significant reductions in respiratory rate and mean arterial pressure. Droperidol caused transient sedation in five of 17 patients, but no other significant changes. Scobutan was associated with an increase in heart rate, but the pupils remained constricted, presumably as a result of morphine. No significant change was produced by saline in the observer’s sedation or pain scores in the control patients, but in four of them there was a slight increase in the patient’s own pain scores (table III), suggesting that the effect of morphine may have begun to decline. All 10 patients in the experimental group wakened and were able to talk coherently within 5–10 min of the infusion of physostigmine. Some described the relief of pain previously experienced and the sudden change in their state of wakefulness. Respiratory rate and the depth of tidal breathing (by observation) and arterial pressure increased after physostigmine, but there was no decrease in the degree of analgesia. Indeed, both the observer’s pain score and that of the patient showed significant reduction (increased analgesia) compared with those after morphine alone (fig. 2).

The pain and sedation scores of the patients who had received physostigmine were all significantly less than those of the saline-treated controls (table III).

### Table III. The effect of physostigmine on analgesia and sedation induced by morphine *Score significantly less than after saline, \( P < 0.01 \)

<table>
<thead>
<tr>
<th>Control</th>
<th>Morphine (30 min)</th>
<th>Physostigmine (5–10 min)</th>
<th>Control</th>
<th>Morphine (30 min)</th>
<th>Saline (5–10 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation score (Observer)</td>
<td>4.00 ± 0.16</td>
<td>2.73 ± 0.17</td>
<td>1.55 ± 0.15*</td>
<td>4.28 ± 0.17</td>
<td>2.36 ± 0.14</td>
</tr>
<tr>
<td>Pain score (Observer)</td>
<td>4.00 ± 0.16</td>
<td>2.73 ± 0.17</td>
<td>1.55 ± 0.15*</td>
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<td>2.36 ± 0.14</td>
</tr>
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### Fig. 2. The effects of physostigmine on the pain and sedation scores of the experimental group of 10 patients.
C = control; M 30 = morphine 30 min; P 10 = physostigmine 10 min, P 40 = physostigmine 40 min. * Scores significantly different by Mann–Whitney \( U \) test, \( P < 0.01 \). Mean score ± SEM indicated by line in hatched area.
the sedation and analgesia scores for morphine, together with the respiratory rates and arterial pressure, were restored to the pre-physostigmine values. The changes in respiratory rate, heart rate and arterial pressure are summarized for the experimental group of patients in Table IV.

Two of the patients (herniorrhaphy and sympathectomy respectively) passed urine 15 min after the injection of physostigmine, having complained previously of urge to micturate without being able to do so. None of the patients complained of nausea or vomiting after morphine or physostigmine. Droperidol 5 mg abolished the nausea of one patient who complained of this before the assessments were commenced.

**DISCUSSION**

The use of extradural anaesthesia in the present study had the advantage of enabling the study to be commenced in patients who were fully aware of their surroundings. They were able to assess clearly their degree of pain and to co-operate with the investigators, in the period immediately after operation.

A total dose of morphine 10 mg/60 kg was needed in all patients to produce a reduction of the pain score from “very severe” or “severe” to “moderate-mild” pain. This degree of analgesia was accompanied in all patients by marked sedation or somnolence, and slight reductions in respiratory rate and arterial pressure.

Physostigmine, by inhibiting the inactivation of acetylcholine, leads to an accumulation of that transmitter and hence to cholinergic stimulation at both peripheral and central receptor sites. It has been found to be effective in the “anticholinergic syndrome” induced by a wide range of drugs that have cholinergic receptor blocking properties (Rumach, 1973). As opiates have been shown to inhibit the release of acetylcholine in both the central and peripheral nervous systems (Weinstock, 1971), it is a reasonable supposition that physostigmine could act as a pharmacological antidote to some of the effects of morphine.

In every patient, physostigmine reversed the sedative effect of morphine, but did not reduce the analgesia. On the basis of the observer’s score, analgesia appeared even to be significantly increased by physostigmine. This, however, may merely reflect the fact that many of the patients who had previously been sleeping or lying with their eyes closed under the influence of morphine (score 2 or 3), woke up and began to talk (score 1). On the other hand, the patient pain score was also less in eight of them after physostigmine was given, and this in turn was significantly less than both pain scores in the control group. Therefore this may be an effect of physostigmine itself on pain sensation. Studies with this drug on experimental pain in animals have shown a significant analgesic effect at doses of 30–130 μg kg⁻¹, which results from activation of cholinergic muscarinic receptors in the central nervous system (Ireson, 1970; Dayton and Garrett, 1973). In experimental pain in human subjects, physostigmine 0.5 mg i.v. increased the threshold to varying intensities of nociceptive stimuli. This effect was associated with increased arousal in the reticular activating system and was thought to result from a dampening of the emotional component of pain (Sitaram, Buchsbaum and Gillin, 1977).

The ionized anticholinergic agent Scobutan prevented all the peripheral muscarinic effects of physostigmine, such as abdominal cramps, bradycardia, sweating or bronchial constriction, without interfering with the analeptic and respiratory stimulant effect.

Previous studies reported nausea and vomiting in a proportion of patients given physostigmine (Toro-Matos et al., 1980). The frequency of nausea and vomiting was particularly small in the study reported by Bidwai, Cornelius and Stanley (1976)
when physostigmine was given to counteract somnolence induced by Innovar, which contains droperidol. In the present series, pretreatment of the patients with droperidol 2.5–5 mg also prevented these effects.

The restoration of the arterial pressure to the premorphone value by physostigmine is in accordance with previous findings in animal experiments (Weinstock, Erez and Roll, 1981). It probably results from an action of the drug in the central nervous system, via the accumulation of acetylcholine on muscarinic receptors (Varagic, 1955), since it is not shared by neostigmine which acts only on peripheral cholinesterase, and is blocked by hyoscine or atropine, which enter the central nervous system (Herz et al., 1965).

Physostigmine has been used to counteract prolonged somnolence or coma induced by different types of pharmacological agents. These include diazepam (Larson, Hurlebert and Wingard, 1977), fentanyl (Bidwai, Cornelius and Stanley, 1976), ketamine (Toro-Matos et al., 1980), tricyclic antidepressants (Burks, Walker and Rumach, 1974). All these drugs have been shown to reduce central cholinergic transmission either directly by blocking receptors of ACh (Atkinson and Ladinsky, 1972) or its release (Jhamandas, Phillis and Finsky, 1971), or indirectly by modulating the action of other neurotransmitters such as GABA, which in turn modify cholinergic activity (Consolo, Garattini and Ladinsky, 1975).

As previously noted in our earlier study and those of others, the effect of physostigmine commences within 5–10 min and lasts 40–60 min when injected i.v. Thus, for a more prolonged reversal of the sedative and respiratory effects of morphine it may be desirable to give a constant infusion of physostigmine during the period that analgesia is required.

ACKNOWLEDGEMENTS

Supported by a grant from the Chief Scientist of the Ministry of Health, Israel

REFERENCES


EFFETS DE LA PHYSOSTIGMINE SUR L’ANALGESIE POSTOPERATOIRE ET LA SOMNOLENCE INDUITES PAR LA MORPHINE

RESUME

Nous avons étudié les effets de 1 mg de physostigmine i.v. sur l’analgésie, la somnolence et la diminution de fréquence respiratoire induites par 10 mg de morphine i.v. pour 60 kg chez 10 patients au réveil d’un acte chirurgical. En 5–10 min, la physostigmine supprimait la somnolence induite par la morphine et rétablissait la fréquence respiratoire à sa valeur d’avant l’injection de morphine. L’analgésie, évaluée par un observateur indépen-
dant et par le patient, était, si elle variait, plutôt augmentée par la physostigmine. L'effet analeptique de la physostigmine durait 40–60 min.

DIE WIRKUNG VON PHYSOSTIGMIN AUF POSTOPERATIVES SCHMERZEMPFINDEN UND SCHLÄFRINGEKT NACH MORPHIUM

ZUSAMMENFASSUNG

Untersucht wurde die Wirkung von Physostigmin i.v. auf die durch 10 mg/60 kg Morphium i.v. hervorgerufene Analgesie, Sedierung und Herabsetzung der Atemfrequenz bei 10 Patienten. Innerhalb von 5 bis 10 min hob Physostigmin die sedierende Wirkung des Morphiums auf und stellte die normale Atemfrequenz wieder her, wie sie vor Opiatgabe bestand. Die Analgesie wurde durch einen unabhängigen Beobachter und von dem Patienten beurteilt, jedoch durch Physostigmin eher verstärkt. Die analeptische Wirkung von Physostigmin dauerte 40 bis 60 Minuten.

EFECTO DE LA FISOSTIGMINA SOBRE LA SOMNOLENCIA Y EL DOLOR POSTOPERATIVO INDUCIDOS MEDIANTE MORFINA

SUMARIO

Se estudiaron los efectos de 1 mg de fisostigmina sobre la analgesia, la sedación y la reducción del ritmo respiratorio como consecuencia de la administración intravenosa de 10 mg por 60 kg de morfina en 10 pacientes en proceso de recuperación de la intervención quirúrgica. En el plazo de 5 a 10 min, la fisostigmina neutralizó el efecto somnoliento de la morfina y restauró el ritmo respiratorio a los valores anteriores a la administración de la droga. La analgesia, si se vio afectada de alguna forma y con arreglo a lo observado por un observador imparcial, aumentó mediante la fisostigmina. El efecto analgésico de ésta duró por espacio de 40 a 60 min.