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EFFECT OF PREOPERATIVE I. M. ADMINISTRATION OF DICLOFENAC ON SUXAMETHONIUM-INDUCED MYALGIA

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SUMMARY

We have studied the effects of preoperative administration of diclofenac on suxamethonium-induced myalgia, plasma met-enkephalin-like activity (E-LA), prostaglandin E_2-like activity (PGE_2-LA), leukotriene C_4-like activity (LTC_4-LA) and histamine-like activity (H-LA). Thirty-four ASA I patients undergoing elective ophthalmic surgery were allocated randomly to two groups to receive either saline placebo or diclofenac 75 mg i.m. 20 min before operation, in a double-blind design. Anaesthesia was induced with thiopentone 5–7 mg kg^{-1} followed by suxamethonium 1.5 mg kg^{-1} and maintained with 67% nitrous oxide and halothane in oxygen. Plasma PGE_2-LA, LTC_4-LA, H-LA and E-LA were measured before premedication, 1 min after the administration of suxamethonium and 24 h after operation. Muscle fasciculations, intubation conditions and postoperative myalgia were graded numerically. Postoperative myalgia in the diclofenac group was significantly ($P < 0.05$) less (47.1%) than in the control group (76.5%). Post-suxamethonium and 24-h concentrations of plasma PGE_2-LA and LTC_4-LA were also significantly ($P < 0.05$) greater than baseline in the control group. Plasma H-LA was increased in both groups after suxamethonium and this increase was significant ($P < 0.05$) in the control group. We conclude that diclofenac reduces significantly the incidence and intensity of suxamethonium-induced myalgia. (Br. J. Anaesth. 1993; **71**: 238–241)

KEY WORDS

Analgesics: diclofenac. Complications: myalgia. Neuromuscular relaxants: suxamethonium.

Several methods have been suggested to prevent suxamethonium-induced muscle pain or to decrease its severity; the most common is pretreatment with a small dose of a non-depolarizing neuromuscular blocking drug before induction of anaesthesia. However, this method is not free of problems such as difficulty with intubation and prolonged neuromuscular paralysis [1–3].

Diclofenac is a potent inhibitor of prostaglandin synthesis and belongs to the group of non-steroidal anti-inflammatory drugs (NSAID) [4]. I.m. diclofenac 75 mg is known to be efficient for the relief of pain in adults [4]. It has been shown also that diclofenac, administered i.m. as single doses of 50–100 mg daily, is an effective analgesic for dental or minor surgical pain, postpartum pain and headache [4]. Absorption is rapid after i.m. administration, with peak plasma concentrations occurring in about 10–30 min [4].

In this study we have evaluated the prophylactic effect of diclofenac on suxamethonium-induced myalgia and on analgesia (met-enkephalin-like activity (E-LA)) and pain mediators (prostaglandin E_2-like activity (PGE_2-LA), leukotriene C_4-like activity (LTC_4-LA) and histamine-like activity (H-LA) of plasma).

PATIENTS AND METHODS

We studied 34, ASA I adult patients undergoing elective ophthalmic surgery (blepharoplasty, dacryocystorhinotomy and plastic repair of the socket). Exclusion criteria included suspected neuromuscular, hepatic or neural disease, anticoagulant therapy, abnormal bleeding tendency, a history of peptic ulceration, known sensitivity to diclofenac and concurrent analgesic medication. Patients gave informed verbal consent to the study, which was approved by our Ethics Committee.

Patients were allocated randomly to two groups. Group 1 ($n = 17$) received saline 2 ml i.m. as premedication and group 2 ($n = 17$) received diclofenac (Voltaren, Ciba–Geigy) 75 mg (≈ 1.5 mg kg^{-1}) i.m. in the gluteal muscle 20 min before operation. The study was conducted in a double-blind fashion. A venous blood sample (baseline) was obtained before this premedication.

A standard anaesthetic technique was used in all patients. General anaesthesia was induced with thiopentone 5–7 mg kg^{-1} and maintained with 67% nitrous oxide and halothane (end-tidal concentration 0.5%) in oxygen. A second blood sample (post-suxamethonium) was obtained 1 min after a bolus dose of suxamethonium 1.5 mg kg^{-1} and the trachea was immediately intubated. A non-depolarizing neuromuscular blocking drug of appropriate duration of action was administered when controlled ventilation of the lungs was required.

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The intensity of visible fasciculations after suxamethonium was graded as: nil (absent); mild (fine fasciculations of the eyes, face, neck or fingers without movement of the limbs); moderate (obvious muscle twitching at more than two sites or movement of limb); severe (vigorous, sustained and widespread fasciculations). Intubation conditions were graded as: excellent (easy and no reaction); adequate (vocal cord movements present); fair (vocal cord movements and moderate reaction); poor (impossible without supplementation).

Blood samples for analysis of plasma PGE_2-LA, LTC_4-LA, H-LA and E-LA were obtained before premedication, 1 min after administration of suxamethonium, and 24 h after operation. Within 1 min of being taken they were centrifuged at 4 °C. Rat fundus muscles were used for assay of PGE_2-LA and guineapig ileal smooth muscles were used for the assays of LTC_4-LA, E-LA and H-LA.

Patients were visited 24 h after operation and questioned about the degree of myalgia, which was graded as: nil (absence of pain); mild (muscle stiffness or pain (on specific questioning) in the nape of the neck, shoulders, and lower chest on deep breathing); moderate (muscle stiffness and pain complained of by the patient spontaneously, requiring analgesia); severe (incapacitating generalized muscle stiffness or pain).

Surgeons were asked about any intra- and postoperative bleeding or other side effects. Postoperative nausea, vomiting, local reaction or pain at injection site, analgesic requirements and mobility were also recorded.

Data were analysed by analysis of variance. Intubating condition, fasciculation and myalgia scores were analysed by Mann–Whitney U test. $P < 0.05$ was considered significant.

RESULTS

There was no significant difference between patient characteristics in the two groups ($P > 0.05$) (table I).

Premedication with diclofenac was associated with a significant reduction in the intensity of myalgia, but not the intensity of visible muscle fasciculations ($P < 0.05$). There was no correlation between the degree of visible fasciculations and the occurrence of muscle pain ($P > 0.05$). Among the patients given diclofenac, only one (5.9%) felt severe pain 24 h after operation, one (5.9%) had moderate pain, six (35.3%) had mild pain and nine (52.9%) had no pain. Three (17.7%) patients in the control group had severe pain, four (23.5%) had moderate pain, six (35.3%) had mild pain and four (23.5%) were free of pain (fig. 1).

Intubating conditions were poor in two (11.8%) patients, adequate in one (5.9%) and excellent in 14 (82.3%) in the control group; poor in one (5.9%), fair in one (5.9%) and excellent in 15 (88.2%) patients in the diclofenac group. These differences were not significant ($P > 0.05$).

Plasma PGE_2-LA was increased significantly in the control group, from 12.91 (SE 1.6) ng ml^{-1} (baseline) to 15.21 (2.3) ng ml^{-1} ($P < 0.05$) after suxamethonium and to 16.13 (2.7) ng ml^{-1} ($P < 0.05$) at 24 h after operation. In the diclofenac group there was an insignificant increase after suxamethonium (from 12.75 (2.0) ng ml^{-1} to 14.60 (2.4) ng ml^{-1}) ($P > 0.05$) which remained almost unchanged ($P > 0.05$) 24 h after operation.

Plasma LTC_4-LA was also increased significantly in the control group, from the baseline value of 8.17 (1.4) ng ml^{-1} to 10.47 (2.0) ng ml^{-1} ($P < 0.05$) after suxamethonium, but decreased to 8.76 (1.5) ng ml^{-1} 24 h after operation. Plasma LTC_4-LA in the diclofenac group was initially 7.44 (1.9) ng ml^{-1}, increased to 8.33 (1.5) ng ml^{-1} after suxamethanium and decreased to 7.5 (1.5) ng ml^{-1} (not significant).

Plasma H-LA was increased in both groups after administration of suxamethonium. While the increase (from 26.8 (2.8) ng ml^{-1} to 31.9 (2.8) ng ml^{-1}) in the control group was significant ($P < 0.05$), that in the diclofenac group (from 31.0 (5.1) ng ml^{-1} to

TABLE I. *Patient characteristics (mean (range or SD))*

	Group 1 (Control)	Group 2 (Diclofenac)
n	17	17
Age (yr)	33.47 (20–59)	31.13 (23–50)
Weight (kg)	58.33 (15.8)	59.13 (14.0)
Sex (M/F)	7/10	9/8
Operation		
Blepharoplasty	8	7
Dacryocystorhinotomy	8	8
Plastic repair of the socket	1	2
Duration of operation (min)	40.6 (14.1)	33.7 (13.5)
Duration of anaesthesia (min)	63.0 (18.9)	55.7 (17.6)

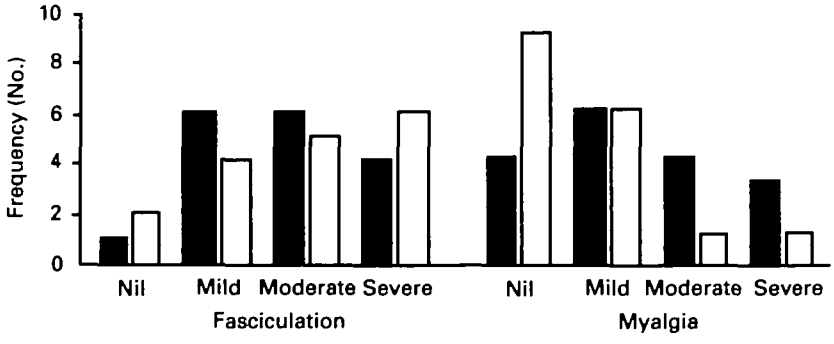

FIG. 1. Frequency of visible muscle fasciculations and postoperative myalgia after administration of suxamethonium in group 1 (control) (■) and group 2 (diclofenac) (□) (mean, SE).

34.6 (4.2) ng ml^{-1}) was not. H-LA values after operation (30 (2.6) ng ml^{-1} in the control group; 30.7 (3.1) ng ml^{-1} in the diclofenac group) were not significantly different from baseline in both groups.

Baseline plasma E-LA in the control and diclofenac groups were 2.24 (0.4) ng ml^{-1} and 2.0 (0.3) ng ml^{-1}, respectively, increasing to 2.79 (0.5) ng ml^{-1} and 2.32 (0.3) ng ml^{-1}, respectively, after suxamethonium ($P < 0.005$ both groups). At 24 h after operation, values had returned to baseline in the diclofenac group (2.23 (0.4) ng ml^{-1}), but remained increased (2.68 (0.5) ng ml^{-1} ($P < 0.05$)) in the control group.

Differences in values of each mediator (plasma PGE_2-LA, LTC_4-LA, H-LA and E-LA) between the control and diclofenac groups were not significant ($P > 0.05$).

No patient received any analgesic or opioid drug during the anaesthetic and postoperative period and administration of diclofenac was not associated with bleeding or side effects. None of the patients complained of pain at the injection site. On the first night after operation, all patients were confined to bed and the next morning they were permitted to mobilize. All were fully active within 30 h and discharged within 48 h.

DISCUSSION

The most common side effect of suxamethonium is probably muscle pain which resembles the aches experienced after unaccustomed exercise.

Although there is often biochemical evidence of muscle damage, with increased plasma concentrations of creatinine kinase and myoglobin after administration of suxamethonium [5, 6], no obvious relationship between pain and biochemical changes has been found [5, 7]. There is also no direct correlation between visible muscle fasciculations and incidence of muscle pains [1, 8]. Collier has reported previously a transient decrease in the serum concentration of calcium 1 min after administration of suxamethonium to patients who experienced muscle pains. He postulated that influx of calcium into the muscle caused an increase in muscle damage and pain [9]. Jackson, Jone and Edwards showed, *in vitro*, that excessive repetitive contractile activity was associated with increased calcium uptake, activation of phospholipase A2, generation of arachidonic acid and synthesis of prostaglandins [10] which may induce delayed-onset inflammation [11, 12]. McLoughlin, Nesbitt and Howe reported a significant reduction in suxamethonium-induced myalgia with soluble aspirin 600 mg given 1 h before operation, and suggested that prostaglandins were responsible for the pain [13]. However, studies from Jackson's laboratory have suggested that lipo-oxygenase products are mediators of calcium-induced intracellular enzyme efflux from skeletal muscle [10, 14], whereas myalgia may be mediated by cyclo-oxygenase products.

In this study, we found that preoperative administration of diclofenac 75 mg reduced suxamethonium-induced muscle pain significantly and did not interfere with intubating conditions. There was no correlation between myalgia and the extent of visible fasciculations. Although patients in the diclofenac group appeared to have more severe fasciculations, this was not statistically significant.

Blood sampling times were chosen as 1 min after administration of suxamethonium (at which time a significant decrease in plasma calcium concentration has been demonstrated [9]) and 24 h after operation (when muscle pains are known to be manifest and a marked increase in plasma creatinine kinase concentration has been reported [5]).

Prostaglandins, leukotrienes and histamine are known to potentiate nociceptive agents and also the formation of oedema [11]. Small doses of PGE_2, in particular, appear to sensitize the pain receptors to stimulation by touch, histamine or bradykinin [15]. PGE_2 also potentiates the oedema-producing capacity of histamine and bradykinin [11, 16]. We observed an increase of 17% in plasma PGE_2-LA and 28% in plasma LTC_4-LA after suxamethonium in the control group in whom there was a high incidence of myalgia. The comparable increase in these substances was not significant in the treatment group, showing a protective effect of diclofenac against a suxamethonium-induced inflammatory response, although the correlation between myalgia and changes in PGE_2-LA and LTC_4-LA does not imply a direct cause–effect relationship. We observed similar changes in both LTC_4-LA and PGE_2-LA; as reported previously, NSAID may block both cyclo-oxygenase and lipo-oxygenase pathways [4, 12]. The protective effect of diclofenac was only partial, suggesting that other substances, such as histamine which was increased in both groups, may affect vasodilatation and oedema formation. This increase in plasma H-LA after administration of suxamethonium was significant in the control group, suggesting an effect of the relatively large concentrations of prostaglandins which have been suggested previously to release histamine from mast cells [17].

Noxious stimulation is known to be an important activator of the normally quiescent endogenous pain suppression system [18, 19], causing direct stimulation of peripheral β-endorphin [20, 21] and met-enkephalin [22]. It has been suggested that excessive secretion of endogenous opioids in response to pain and stress might be associated with "spill-over" of opioid peptides into the systemic circulation, with the possibility that their concentration in plasma may be taken as an indicator [23]. In agreement with these studies, we observed a significant increase in plasma E-LA after induction of anaesthesia in both groups. The persisting increased enkephalin-like activity in the control group after operation may be explained by the relatively great concentrations of the potent hyperalgesic mediators, PGE_2 and LTC_4.

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