

EFFECT OF I.V. LIGNOCAINE ON PAIN AND THE ENDOCRINE METABOLIC RESPONSES AFTER SURGERY

K. BIRCH, J. JØRGENSEN, B. CHRÆMMER-JØRGENSEN AND H. KEHLET

Apart from its extensive use in local anaesthesia, lignocaine may have other potential therapeutic uses as a result of its membrane stabilizing effect and ability to suppress irritable foci in various organs. Thus, the use of lignocaine in the treatment of ventricular arrhythmias and epileptic seizures is well documented. In addition, a protective effect on the ischaemic brain has been suggested because of the inhibition of oxygen and glucose consumption in the brain (Astrup, Skovsted et al., 1981; Astrup, Sørensen et al., 1981).

Potential advantages of i.v. lignocaine during anaesthesia and surgery have been suggested in regard to a decrease in anaesthetic requirements (Phillips et al., 1960; Himes, DiFazio and Burney, 1977), the production of stable clinical anaesthesia (Soares, 1952; Blancato, Peng and Alonsabe, 1969; Knight et al., 1980) and for relief of pain after surgery (de Clive-Lowe, Spencer Gray and North, 1954; Desmond, 1957; de Clive-Lowe, Desmond and North, 1958; Bartlett and Hutaserani 1961). However, the possible effect of i.v. lignocaine on postoperative pain has been supported mainly by uncontrolled observations. In a single controlled study on experimentally induced ischaemic pain, no effect was observed on pain threshold or tolerance at blood concentrations of 1-3 $\mu\text{g ml}^{-1}$ (Rowlingson et al., 1980).

Therefore, the present study was undertaken to investigate, under controlled conditions, the possible effect of i.v. lignocaine on postoperative pain, and the adrenocortical and hyperglycaemic responses to abdominal hysterectomy.

SUMMARY

Pain intensity, and blood glucose and plasma cortisol concentrations were measured following abdominal hysterectomy in 18 patients allocated randomly to receive either i.v. lignocaine 1.5 mg kg⁻¹ plus 2 mg kg⁻¹ h⁻¹, or saline. The administration of lignocaine resulted in plasma concentrations between 1.5 and 2.0 $\mu\text{g ml}^{-1}$ during the 2-h study period. However, the administration of lignocaine i.v. had no effect on the intensity of pain after surgery, or on the adrenocortical and hyperglycaemic responses to surgery.

PATIENTS AND METHODS

Eighteen otherwise healthy women undergoing elective abdominal hysterectomy were studied. Informed consent to participate was obtained from all patients and the design of the study was approved by the ethics committee of Copenhagen County Hospitals.

All patients received a general anaesthetic which included the administration of thiopentone, suxamethonium, pancuronium, and halothane and nitrous oxide in oxygen. Diazepam 0.2 mg kg⁻¹ by mouth was used for premedication. Glucose was not given during the study. No analgesics were given during surgery.

The 18 patients were allocated randomly to receive, under double-blind conditions, either an i.v. injection of lignocaine 1.5 mg kg⁻¹ as a bolus plus an i.v. infusion of 2 mg kg⁻¹ h⁻¹ for 2 h, or saline in the same volumes for injection and infusion. The administration of lignocaine or saline started following the first request for pain relief after surgery.

Age (mean 41 \pm 2 yr in the lignocaine group, and 42 \pm 2 yr in the saline group) and weight (62 \pm 4 and 68 \pm 3 kg, respectively) did not differ

K. BIRCH, M.D., J. JØRGENSEN, M.D. (Department of Gynecology and Obstetrics); B. CHRÆMMER-JØRGENSEN, M.D. (Department of Anaesthesiology); Glostrup Hospital, DK-2600 Glostrup, Denmark. H. KEHLET, M.D., Department of Surgical Gastroenterology, Hvidovre Hospital, Hvidovre, Denmark. Accepted for Publication: September 1, 1986.

Correspondence to K. B.

between groups ($P > 0.05$). All patients were without cardiovascular or hormonal diseases; none was receiving any medication, including contraceptives.

Blood samples were taken from a central vein just before extubation of the trachea and every 20 min until the patient requested pain relief. From this time blood samples were taken at 0, 10, 20, 30, 40, 60, 80, 100 and 120 min after the injection of, and the start of the infusion of, lignocaine or saline.

When the patients requested pain relief, pain intensity was measured using a 10-cm visual analogue scale at the same times as blood sampling. If the patients did not obtain any pain relief (i.e. the pain intensity score had changed less than 1 cm) 30 min after starting the lignocaine or saline infusion, the patients received morphine 0.15 mg kg⁻¹ i.v. followed by a supplementary dose, if necessary.

The lignocaine-saline infusion, blood sampling and visual analogue pain scoring continued irrespective of the administration of morphine.

Blood glucose concentration was measured by a routine glucose oxidase method and cortisol concentration by a commercial radioimmunoassay. Plasma lignocaine concentration was measured by gas chromatography (by Dr Arne Hansson, Department of Clinical Chemistry, Malmö Almänna Sjukhus, Malmö, Sweden).

Statistical analysis was performed using Student's *t* test for paired and non-paired variables. $P < 0.05$ was considered significant. All values are reported as mean \pm SEM.

RESULTS

There was no difference between the lignocaine group and the saline group with regard to time from skin incision to extubation of the trachea (81 ± 3 and 86 ± 8 min, respectively) ($P > 0.05$) or in the time from extubation of the trachea to the first request for pain relief and, therefore, the start of the infusion of lignocaine or saline (37 ± 4 and 33 ± 6 min, respectively) ($P > 0.05$).

Similarly, no differences were observed in the administration of morphine between the lignocaine and saline groups (8.3 ± 0.7 mg supplemented with 3.9 ± 1.4 mg and 10.0 ± 0.7 mg supplemented with 5.7 ± 1.3 mg, respectively) ($P > 0.05$).

Pain intensity scores (mean \pm SEM) in the two groups are shown in figure 1. In the saline group,

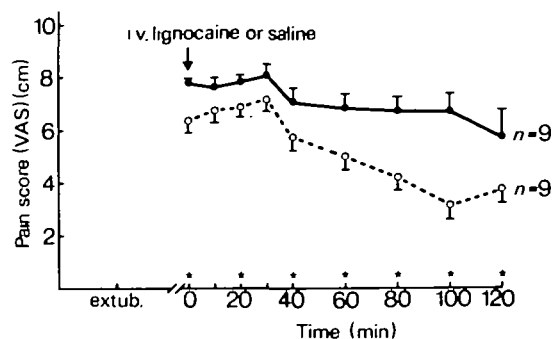


FIG. 1. Pain scores (mean \pm SEM) during the first 120 min after abdominal hysterectomy in patients receiving either an i.v. injection of lignocaine 1.5 mg kg⁻¹ plus an i.v. infusion of 2 mg kg⁻¹ h⁻¹ for 2 h (—) or saline (---). Patients who felt no pain relief 30 min after initiation of lignocaine or saline infusion received i.v. morphine 0.15 mg kg⁻¹ followed by a supplementary dose if necessary. *Significant differences between groups ($P < 0.05$).

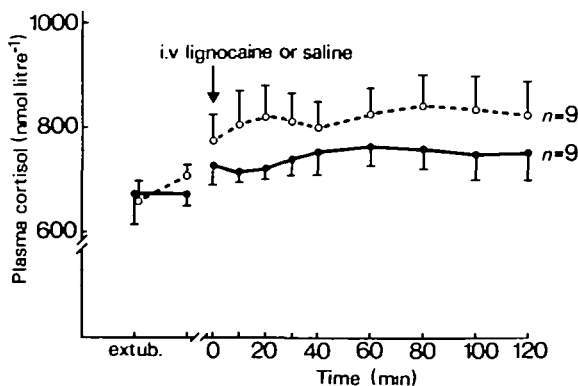
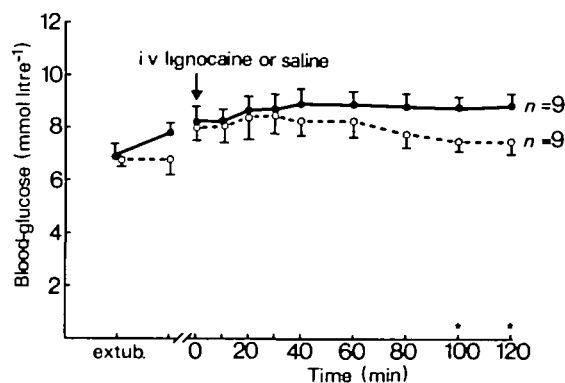


FIG. 2. Blood glucose and plasma cortisol concentrations (mean \pm SEM) after abdominal hysterectomy; same procedure as figure 1. — = Lignocaine; --- = saline. * $P < 0.05$.

pain scores were significantly lower than in the lignocaine group at the first request for pain relief and, therefore, on the initiation of the infusion of lignocaine or saline. However, during the first 30 min after the administration of lignocaine or saline, pain scores were constant in both groups. Thereafter, a slight decrease in pain intensity was observed in both groups following the administration of morphine. However, pain scores were higher in the lignocaine group than in the saline group throughout the study period.

Changes in plasma cortisol and blood glucose concentrations are shown in figure 2. Similar concentrations were observed following extubation of the trachea in both groups, and the administration of lignocaine or saline had no effect on the plasma concentrations of cortisol or glucose during the following 2 h. Plasma cortisol concentrations were slightly (but insignificantly) higher in the saline group and blood glucose concentrations lower 100 and 120 min after the start of infusion in the saline group compared with the lignocaine group ($P < 0.05$).

Plasma concentrations of lignocaine were between 1.5 and 2.0 $\mu\text{g ml}^{-1}$ (fig. 3).

No patient experienced any complications or side effects of the lignocaine injection and infusion.

DISCUSSION

It has been demonstrated previously in uncontrolled studies that i.v. lignocaine in doses of 400–1000 mg produces good pain relief after surgery (de Clive-Lowe, Spencer Gray and North, 1954; Desmond, 1957; de Clive-Lowe,

Desmond and North, 1958; Bartlett and Hutaserani, 1961). However, in the present controlled double-blind study, no effect of i.v. lignocaine was observed on pain intensity at the time of first postoperative request for pain relief. Furthermore, the adrenocortical and hyperglycaemic responses were not influenced. The explanation for these discrepancies may be partly the different designs of the studies and partly the different dosages of lignocaine used as our patients received on average 350 mg of lignocaine compared with the 400–1000 mg given in the above-mentioned studies. However, if the administration of lignocaine was effective in the treatment of postoperative pain, there might be a risk of toxic symptoms with the higher doses. In our patients plasma concentrations of lignocaine were well below toxic values. It may be argued that, in our study, lignocaine was administered following a request for pain relief (in the postoperative period), in contrast to other studies in which the lignocaine was administered during the operation (de Clive-Lowe, Spencer Gray and North, 1954; Desmond, 1957; de Clive-Lowe, Desmond and North, 1958; Bartlett and Hutaserani, 1961). However, in another controlled study in which lignocaine (in doses between 250 and 730 mg) was administered during operation (Phillips et al., 1960), a significant reduction in anaesthetic requirement was observed, but no effect was demonstrated on the requirement for analgesics in the first 24 h after surgery. Pain intensity scores were not measured in that study.

The possible influence of i.v. lignocaine on other forms of acute pain has also been disappointing. Thus, lignocaine had no effect on pain threshold or pain tolerance to tourniquet-induced ischaemia when lignocaine plasma concentrations were 1–3 $\mu\text{g ml}^{-1}$ (Rowlingson et al., 1980). Similar results were found during the i.v. infusion of lignocaine under uncontrolled conditions in patients with neuralgic pain during tourniquet-induced pain when plasma lignocaine concentrations were less than 3 $\mu\text{g ml}^{-1}$ (Boas, Covino and Shahnarian, 1982). However, clinical pain before ischaemia was suppressed by lignocaine, and when plasma concentrations of lignocaine were higher both tourniquet pain and clinical pain were decreased (Boas, Covino and Shahnarian, 1982).

Although uncontrolled observations suggest that i.v. lignocaine infusion with plasma concentrations greater than 3 $\mu\text{g ml}^{-1}$ is beneficial in acute, including postoperative, pain, our double-blind

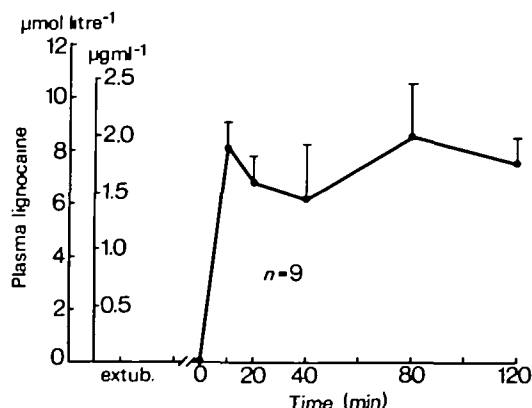


FIG. 3. Plasma lignocaine concentrations (mean \pm SEM) after abdominal hysterectomy in patients receiving i.v. injection of lignocaine 1.5 mg kg^{-1} plus an i.v. infusion of 2 mg $\text{kg}^{-1} \text{ h}^{-1}$ for 2 h.

controlled study failed to document any reduction in pain intensity or adrenocortical and hyperglycaemic responses to abdominal hysterectomy when plasma lignocaine concentrations were 1.5–2.0 $\mu\text{g ml}^{-1}$.

Although negative, our results may be of interest since there has been, in recent years, increasing interest in the systemic effects of the administration of lignocaine. Several studies have shown lignocaine to have some influence on the inflammatory response to injury on aspects of coagulation (thrombocyte aggregation) and in immunological function. We believe that some of these areas may very well be of clinical interest in the years to come.

ACKNOWLEDGEMENT

The study was supported by a grant from Astra Läkemedel, Södertälje, Sweden.

REFERENCES

- Astrup, J., Skovsted, P., Gjerris, F., and Sørensen, H. R. (1981). Increase in extracellular potassium in the brain during circulatory arrest: effects of hypothermia, lidocaine, and thiopental. *Anesthesiology*, 55, 256.
- Sørensen, P. M., and Sørensen, H. R. (1981). Inhibition of cerebral oxygen and glucose consumption in the dog by hypothermia, pentobarbital, and lidocaine. *Anesthesiology*, 55, 263.
- Bartlett, E. E., and Hutaserani, O. (1961). Xylocaine for the relief of postoperative pain. *Anesth. Analg.*, 40, 296.
- Blancato, L. S., Peng, A. T. C., and Alonsabe, D. (1969). Intravenous lidocaine as an adjunct to general anesthesia for endoscopy. *Anesth. Analg.*, 48, 224.
- Boas, R. A., Covino, B. G., and Shahnarian, A. (1982). Analgesic responses to i.v. lignocaine. *Br. J. Anaesth.*, 54, 501.
- de Clive-Lowe, S. G., Desmond, J., and North, J. (1958). Intravenous lignocaine anaesthesia. *Anaesthesia*, 13, 138.
- Spencer Gray, P. W., and North, J. (1954). Succinylcholine and lignocaine by continuous intravenous drip. *Anaesthesia*, 9, 96.
- Desmond, J. (1957). A new concept of general anaesthesia evolved from the use of xylocaine hydrochloride administered by the intravenous route. *Can. Serv. Med. J.*, 13, 93.
- Himes, R. S., DiFazio, C. A., and Burney, R. G. (1977). Effects of lidocaine on the anesthetic requirements for nitrous oxide and halothane. *Anesthesiology*, 47, 437.
- Knight, P. R., Kroll, D. A., Nahrwold, M. L., Denlinger, K., Kirsh, M., Welter, L. O., Hill, A. G., Cohen, P. J., and Ronfeld, R. A. (1980). Comparison of cardiovascular responses to anesthesia and operation when intravenous lidocaine or morphine sulfate is used as adjunct to diazepam–nitrous oxide anesthesia for cardiac surgery. *Anesth. Analg.*, 59, 130.
- Phillips, O. C., Lyons, W. B., Harris, L. C., Nelson, A. T., Graff, T. D., and Frazier, T. M. (1960). Intravenous lidocaine as an adjunct to general anesthesia: a clinical evaluation. *Anesth. Analg.*, 39, 317.
- Rowlingson, J. C., DiFazio, C. A., Foster, J., and Carron, H. (1980). Lidocaine as an analgesic for experimental pain. *Anesthesiology*, 52, 20.
- Soares, E. L. (1952). General anesthesia with pentothal–Novocain. *Anesth. Analg.*, 31, 402.