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Lignocaine and headache: an electrophysiological study in the cat with supporting clinical observations in man

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Abstract Chronic daily headache (CDH) is a particularly difficult type of headache to manage, with an uncertain pathophysiology. Intravenous administration of lignocaine has been suggested as a possibly useful option in the control of this syndrome. We have surveyed prospectively patients with CDH (selected for this study as those with 6 or more months of continuous pain with at least weekly exacerbations that, taken in isolation, would fulfil International Headache Society diagnostic criteria for migraine without aura). Intravenous lignocaine (2 mg/min) by infusion over a 2-day period rendered 26% of patients pain free, with a further 42% having at least a 50% improvement in the pain. Continued benefit was associated with commencement of prophylaxis with a tricyclic antidepressant or monoamine oxidase inhibitor after completion of the lignocaine infusion. In an animal model of craniovascular nociception, using electrical stimulation of the superior sagittal sinus and recording of single unit activity and sensory evoked potentials in the spinal trigeminal nucleus in the upper cervical spinal cord of the anaesthetised cat, the effect of lignocaine was examined. Lignocaine reduced both the probability of cell firing and the size of the trigeminal evoked potential in the animals studied. The reduction was both substantial (more than 25% in each case) and dose-dependent. Taken together the data suggest that CDH is likely to be a disorder of central craniovascular nociceptive control and that lignocaine acts to interrupt a part of the pathway involved but is unlikely to act at the central generator of the disorder.

Key words Chronic daily headache · Lignocaine · Trigeminal · Headache pathophysiology

Introduction

One of the most difficult clinical type of headache is that of the patient with what has been termed *chronic daily migraine* [1] or *chronic daily headache* (CDH) [2, 3]. Such patients typically have daily continuous headache and for many this is punctuated by regular, sometimes daily, exacerbations of a more severe headache that may fulfill standard International Headache Society (IHS) Criteria for migraine [4]. These patients very often make excessive use of compound analgesics, such as those with codeine phosphate [5], and may often have psychological problems or stressors that aggravate their difficulties. They do not fit easily into any of the current IHS diagnostic categories and it can be suggested with considerable practical justification that a new accomodating category should be found [6]. A considerable part of the problem in studying these patients is that CDH represents an heterogeneous group of head pain problems arising in a number of ways. In these studies we have sought to make inferences about some of the possible mechanisms at work in CDH by comparing and contrasting clinical observations and experimental studies. We have chosen deliberately to

restrict the patients to a more narrowly defined group to make a more homogeneous cohort to study.

The practical problem in these patients is that of therapy. We have reported in an open-label comparative review that intravenous lignocaine can be of benefit to a group of these patients [1] as others have suggested [7]. In a double-blind study of more typical migraine patients lignocaine (1 mg/kg) was not effective [8]. The extent of the pathophysiological overlap of these patients with CDH and those with more typical migraine is not clear and the lack of a response in typical migraineurs may not imply the same outcome in CDH.

Lignocaine is a local anaesthetic, the action of which derives from blockade of fast Na^+ channels. It has been used more recently in chronic pain states [9] and particularly in post-herpetic neuralgia [10]. We have therefore examined both the clinical and physiological aspect of the possible efficacy of intravenous lignocaine by reviewing our recent experience with lignocaine specifically in CDH patients, restricted in character by sampling definition, and by examining its effect in an animal model of trigeminal nociception, sagittal sinus stimulation in the cat [11]. The clinical arm of the study does not serve as a trial of lignocaine since it is not blinded but rather serves to compare and contrast with the electrophysiological studies.

Materials and methods

Clinical observations

The patients reviewed were all admitted to our Neurology Unit with what we shall term CDH. This term has no universal meaning and so for this study patients were restricted to make a more homogeneous group. Each had a daily headache present for more than 6 months with exacerbations at least once a week of a more severe headache that taken on its own would fulfill IHS criteria for an acute attack of migraine. There were 19 patients available for study, of whom 2 had been regular users of ergotamine-containing preparations (2–6 mg/day) and 16 patients had been having frequent (at least weekly) meperidine (pethidine) injections. In effect all patients had transformed migraine that would be classified by Pfaffenrath and colleagues [6] as either primary CDH evolved from migraine or secondary CDH related to ergotamine overuse. The patients underwent a standard protocol of lignocaine with an initial bolus of 1 mg/kg followed by an infusion of 2 mg/min for the next 2 days. They were evaluated for the outcome at the endpoint immediately post-infusion. This point was chosen since the electrophysiological outcome was evaluated after acute infusion and chronic data could not be obtained. Patients were asked to rate the change as either headache free, headache (pain) 50% improved or no change. More involved analyses of the patients was not attempted since the study's purpose was for comparison with the electrophysiological data and not as a clinical trial.

Animal studies

Five female cats weighing 2.7, SD 0.2 kg were anaesthetised initially with 1.5% halothane and then α-chloralose (60 mg/kg, intraperitoneally) and prepared for physiological monitoring. The femoral artery and vein were cannulated in order to measure blood pressure and heart rate and provide access for drug administration, respectively. Blood pressure, heart rate and pupillary reaction to noxious pinching of the limb were used to determine the need for supplementary anaesthesia. The animals were endotracheally intubated, ventilated with 40% oxygen and paralysed after the surgical procedures (repeated doses of gallamine triethiodide 6 mg/kg intravenously as required). Body temperature and end-expiratory CO_2 were monitored and maintained within physiological limits. After mounting in a stereotactic frame, a circular midline craniotomy (2 cm in diameter) and C1/C2 laminectomy were performed for access to the superior sagittal sinus (SSS) and the recording site in the C2 spinal cord. Possible artefacts from arterial pulsation and respiration were reduced by bilateral pneumothoraces, suspension of the thoracic spinal processes, clamping of the C1 lateral spinal processes and covering the cervical spinal cord with a layer of agar gel.

The dura and falx adjacent to the SSS were dissected over 10 mm and the sinus suspended over bipolar platinum hook electrodes. To prevent dehydration and for electrical insulation against the cortex a paraffin bath was built with a dam of dental acrylic around the craniotomy and additionally a small polyethylene sheet inserted under the SSS. To activate trigeminal primary afferents, the SSS was stimulated with a Grass S88 stimulator with stimulus isolation unit (150 V, 250 μs, 0.3 Hz; SIU5A). Tungsten-in-glass microelectrodes (tip length/diameter: 50/15 μm, impedance: < 200 kΩ) were lowered into the dorsolateral spinal cord 4–5 mm caudal to the mid-point of the C2 rootlets between 600 and 1200 μm below the surface with a hydraulic micropositioner (Kopf, model 650, USA). Electrical responses were amplified (NeuroLog, total system gain 20000–30000) and lowpass filtered (NeuroLog, high cut-off frequency 5.5 kHz) to prevent aliasing. The signal from the amplifier was passed to the analog input of an A/D converter (LabMaster, Ohio) in an IBM-compatible microcomputer (80386/80387 based) for simultaneous analysis online of single units and field potentials by a custom written program (Microsoft C).

To obtain somatosensory field potentials the raw data were high pass filtered online with a digital second-order Butterworth filter (cut-off frequency 250 Hz) to remove effects from superimposed action potentials on the amplitudes of the slow potentials and averaged over 25 or 100 repetitive recordings (sweep length 50 ms). Single unit activity was analysed after digital online high pass filtering (cut-off frequency 500 Hz) and passing a digital window discriminator to create a post-stimulus histogram over 25 or 100 recordings (sweep length 50 ms) to identify linked responses. Baseline recordings with 100 averages each were repeated at least three times to ensure that single unit and field potential respones in the spinal cord to SSS stimulation were reproducible over time. Lignocaine (2%; Delta West Ltd, Australia) was administered as an intravenous bolus injection in increasing doses ranging from 1 mg/kg to 10 mg/kg with 0.9% saline as the vehicle. After the injection of lignocaine recordings of 25 sweeps were repeated after 1, 2, 5, 10, 15 and 30 min. Lignocaine injections were only given when the systemic blood pressure was above 120 mmHg. Throughout the experiments the electrophysiological signals, blood pressure and heart rate were pulse code modulated (Vetter, 16 Channel) and stored on video tape for documentation. After the experiment animals were killed by intravenous KCl.

After death another 25 responses were elicited to obtain slow potentials that only consisted of the artefact and subtracted from all previous recordings before determining the peak-to-peak amplitudes in order to increase the specificity of the analysis. Responses to lignocaine were compared using a Spearman rank correlation coefficient [12] and assessed at the $P < 0.05$ level for significance.

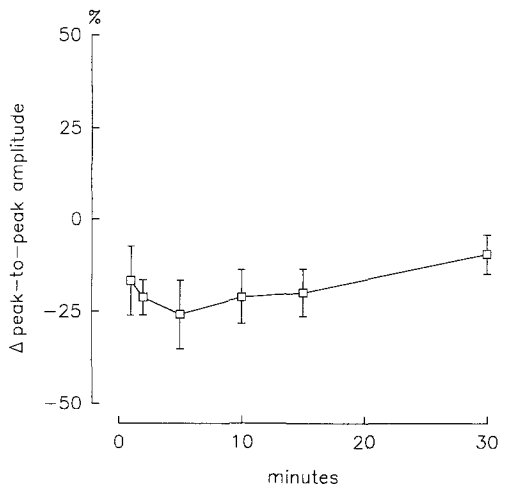

Fig. 1 The effect of lignocaine on trigeminal evoked potentials in the upper cervical spinal cord is illustrated as a function of time. At time zero lignocaine (5 mg/kg, intravenous) was administered and the response to stimulation of the superior sagittal sinus monitored at intervals (time on the *abscissa*) up to 30 min when there had usually been substantial recovery to baseline. The *ordinate* represents the percentage reduction in the peak-to-peak amplitude of the trigeminal evoked potential and the mean reduction with SEM envelopes is shown

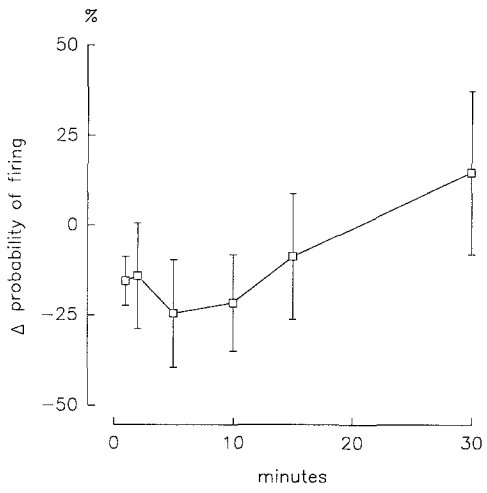

Fig. 2 The effect of lignocaine on single unit activity in the upper cervical spinal cord is shown following the same course as described in Fig. 1. Special solftware written for these studies allowed simultaneous monitoring of evoked potentials and single unit activity in any animal studied (see Materials and methods). Again there is an inhibition of neuronal activity soon after lignocaine infusion that returns to baseline by 30 min. The *ordinate* represents the percentage change from baseline in the probability of cell firing

Results

Clinical observations

Of the patients studied, 17 were female and 2 male with a mean age of 50, SD 6 years and a mean duration of headache of 17, SD 3 months. Most patients had either nausea (100%), photophobia (95%) or phonophobia (47%) during exacerbations of the headache, with 12 having bilateral pain and 7 unilateral pain. In all patients headache during the severe phase was exacerbated by head movement. The severe headaches were often pounding or throbbing in character (10 patients). Of the patients treated, 26% had complete resolution of pain on lignocaine, while 42% had improvement in headache they rated as 50% or more better. The remainder (32%) had no change at all during the infusion. At follow-up none of the patients with partial improvement had continuing benefit unless they had been started on prophylaxis (amitriptyline, dothiepin or phenelzine) when the infusions had ceased. Of those whose headaches had resolved or improved during the infusion half had relapsed despite prophylaxis.

Animal studies

Physiological variables of the five animals were kept within normal limits. For the animals included in the analysis, arterial blood gas data were normal: pH 7.33, SD 0.03, PCO_2 35, SD 2, PO_2 215, SD 11. Injection of 5 mg/kg lignocaine led to a reduction of baseline field potential amplitudes in all animals, reaching a maximum of 26, SD 9% after 5 min (Fig. 1; $P < 0.05$) and a reduction in the probability of firing for single units by 25, SD 14% (Fig. 2). After 30 min linked responses returned to control values. Typical recordings of single unit activity for controls and following injection of 5 mg/kg lignocaine are shown in Fig. 3. The effect of lignocaine on the latencies of the maximum amplitude of field potentials and firing single units was negligible (< 1.2 ms).

The effects of lignocaine on field potentials elicited by electrical stimulation of the SSS were dose dependent (Fig. 4). Doses higher than 1 mg/kg led to a decrease in peak-to-peak field potential amplitudes and probability of firing of single units. Doses higher than 5 mg/kg (7.5–10 mg/kg) did not suppress the response further but had longer lasting effects often accompanied by hypotension. In animals that showed a decrease in systemic blood pressure greater than 25 mmHg after administration of lignocaine, hypotension was induced after blood pressure had returned to normal by inducing haemorrhage (20–50 ml). This did not reproduce the effects of lignocaine on the electrophysiological responses to SSS stimulation.

Discussion

These data demonstrate that the local anaesthetic lignocaine can ameliorate continuous headache in a group of

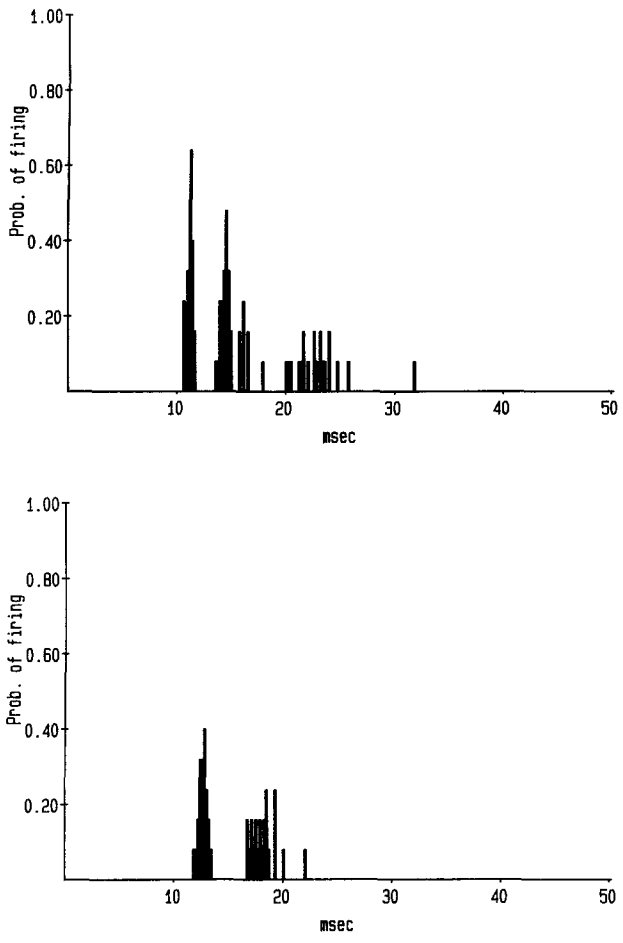

Fig. 3 A, B Original recordings of single unit activity from the caudal-most trigeminal nucleus following electrical stimulation of the superior sagittal sinus. The *ordinate* represents the probability of firing and the time on the *abscissa* (ms) is marked from the initial stimulation for a sweep of 50 ms. The control response is shown in **A** with the response after lignocaine (5 mg/kg, intravenous) in **B**

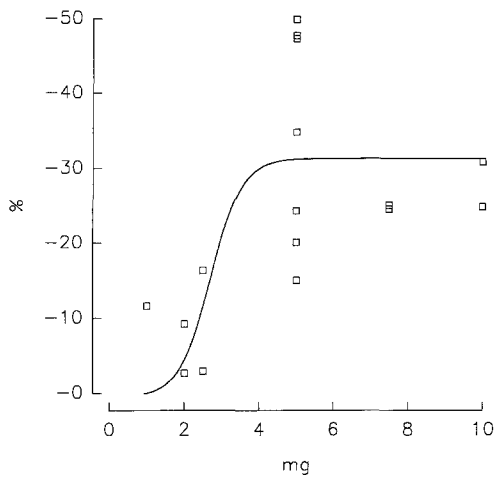

Fig. 4 Dose-dependent effects of lignocaine on trigeminal evoked potentials in the upper cervical spinal cord. Increasing doses of intravenous lignocaine reduce the peak-to-peak amplitude of the trigeminal evoked potential arising from superior sagittal sinus stimulation cat. The *ordinate* represents the percentage reduction in the peak-to-peak amplitudes with individual doses plotted for each animal

patients and that an animal model indicates that the mechanism may be inhibition of neuronal activity in the spinal trigeminal nucleus. Lignocaine does not improve all headaches, nor does it silence all cell firing in the trigeminal nucleus. Furthermore, since the elctrophysiological changes are transient and reversible, it is unlikely that the locus of the problem in CDH lies in the trigeminovascular neurones or their peripheral projections.

The animal studies as they have been conducted cannot directly distinguish between central and peripheral effects, and serum lignocaine levels were not determined. However, the dosages used (1–10 mg/kg) compare well with those used in clinical studies and are an order of magnitude smaller than those required for axonal blockade [13]. Peripheral effects with low doses (< 10 μg/ml) of lignocaine have only been demonstrated [14] on tonic discharges of injured A-delta and C fibres and free nerve terminals. This is unlikely to be the cause for the observed trigeminal inhibition seen in our studies since extreme care was taken not to damage or even touch the stimulation site. Furthermore, any interaction with transduction mechanisms at free nerve endings would have been bypassed by the supramaximal stimulation. Therefore, a central action of lignocaine on trigeminal neurones may be postulated, similar to direct effects at a central spinal level as previously described [15]. The dose-dependent inhibition of trigeminal central neurones would also favour a central effect rather than an axonal mechanism which should be all-or-nothing as lignocaine levels move over a crucial concentration. A further remarkable parallel between the animal studies reported here and man is in the time course of the lignocaine-induced changes. Maciewicz and colleagues have reported [7] that lignocaine (100 mg intravenous bolus) produces an amelioration of headache in 20 min in patients with acute vascular headache and some other forms of head pain such as, post-carotid endarterectomy pain. In the animal model described here the inhibition of trigeminal evoked activity has an almost identical time course emphasising the relevance of our animal data to the human situation.

What is the headache entity described here as chronic daily headache? CDH is not a single entity; rather it is a clinical syndrome with certain features, the cardinal of which is virtually continuous headache. For this study we have used perhaps the most malignant group of patients whose headaches have transformed from migraine with or without the further aggravation of ergotamine overuse. The landmark paper in this field is that of Mathew et al. [16], who called attention to the fact that with time severe

episodic headache could transform to a daily headache. In one large study up to 80% of patients with daily headache had been subject to intermittent headache earlier in life [2]. There is little doubt that in practice a certain group of patients present with a daily usually constricting headache that is punctuated by exacerbations of moderate or severe headache, sometimes unilateral and throbbing. Such exacerbations are often associated with nausea, photophobia or phonophobia and made worse by movement. If these patients simply reported their episodic pain they could be classified as migraine; yet they plainly do not have strictly episodic pain, since some pain persists, nor do they have status migrainosis by IHS criteria [4]. The syndrome of CDH is often the product of true episodic migraine that has evolved or transformed [17] and can often be very difficult to treat. The same syndrome may evolve from tension-type headache, or as a sequela to head injury or infection [6]. Sometimes the tag of tension-vascular headache is applied to this syndrome, but this offers no more useful pathophysiological information on the nature of the headache. The patients included in this report are operationally defined in the Materials and methods section and a strong case can be mounted for a separate category for them in any revision of the IHS diagnostic criteria [18].

This study sought to draw inferences from the human data, not to provide a therapeutic trial of lignocaine. Lignocaine was only partially effective in relieving headache and blocking neuronal discharge in the animal study. Since only patients subsequently treated with centrally acting drugs, such as tricyclic antidepressants or monoamine oxidase inhibitors, showed sustained improvement, it is unlikely that the lignocaine had its effect at the site of the central generator of the headache. Other treatments of CDH syndromes that have been reported to be useful, such as naproxen [19] or sumatriptan [20], are assumed to act at a peripheral site of action. There are, however, certainly receptors in the trigeminal nucleus that can mediate inhibitory effects in that nucleus for both sumatriptan [21] and acetylsalicylic [22]. Moreover, dihydroergotamine has also been used in this syndrome with considerable success [23] and there are certainly receptors in the trigeminal nucleus that are inhibitory [24] and located in the same region as the cells sampled in this study [25]. In many of these patients the overuse of compound analgesics, acting at central opiate receptors, or ergots, that may also act centrally [25], plays a role in the development of more headaches and their withdrawal ameliorates headache in 80% of patients [26]. These clinical observations argue further for a central nervous system origin. Indeed, the fact that other chronic pain states [9], including post-herpetic neuralgia [10], that are thought to have a centrally mediated contribution, are also favourably affected by lignocaine, is consistent with an ultimately central origin for many forms of CDH.

In summary, these data indicate that lignocaine is capable of ameliorating CDH, as expressed as the syndrome of daily dull pain punctuated by severe episodes that would satisfy diagnostic criteria for migraine without aura. Further in an animal model of craniovascular pain evoked by electrical stimulation of the SSS, intravenous lignocaine blocks central trigeminal neurones in a dose-dependent manner. Taken together these data point to the importance of central generating mechanisms in this extremely refractory form of chronic head pain.

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