

## ANALGESIC RESPONSES TO I.V. LIGNOCAINE

R. A. BOAS, B. G. COVINO AND A. SHAHNARIAN

## SUMMARY

The analgesic effect of i.v. lignocaine was evaluated in five patients with clinical neuralgic pain of varying aetiology. The response was compared with that on concurrently-induced ischaemic pain, initially of the same intensity. Following a high dose infusion of  $3 \text{ mg kg}^{-1}$  (lignocaine concentrations greater than  $3 \mu\text{g ml}^{-1}$ ) both pains were decreased, clinical pain to a significantly greater extent. Thereafter, at lower doses and blood concentrations, lignocaine was without effect on ischaemic pain, but almost totally suppressed the same patient's clinical pain. The results suggest a divergence in the specificity of the analgesic action of lignocaine i.v. according to the nature of the pain-inducing process. Disorders manifesting as deafferentation or central neuralgias appear to be affected favourably by lignocaine i.v., whereas pain of peripheral origin is unaffected by lignocaine, except at blood concentrations which approach toxic values.

The ability of lignocaine to suppress irritable foci in the heart and brain (Covino and Vassallo, 1976), has proved to be of value in the treatment of ventricular arrhythmias and epileptic seizures. Pain associated with neurological deafferentation may have spinal electrogram patterns characterized by high-frequency burst discharge activity in neurons of the central nervous system (Loeser, Ward and White, 1968; Anderson et al., 1971). Since this discharge activity may be similar in nature to ectopic activity in the heart or epileptic activity in the cerebral cortex it seemed worthwhile considering the use of lignocaine i.v. as an analgesic agent in patients presenting with appropriate features of neurological deafferentation disorders. Some support for this concept could be derived from earlier clinical experience in the treatment of pain of postherpetic neuralgia (Hatangdi, Boas and Richards, 1976).

## PATIENTS AND METHODS

Five patients who had given written consent were chosen to participate in this initial investigation. All were from the Pain Clinic at the University of Massachusetts Medical Center. Each patient had severe pain for a minimum of 6 months before the study and was considered to have a disorder of a

dominant neuralgic pattern with elements of central or spinal pain as judged by the known pathology and symptomatic features. The clinical disorders demonstrated by the five patients are shown in table I together with the ages and weights of the patients.

Catheters were placed in the antecubital vein and radial artery in one arm and a pneumatic tourniquet applied above the elbow on the opposite arm. The patients were trained to use a 10-cm linear analogue scale for depicting pain intensity. At the start of the study, each patient was asked to score the intensity of their clinical pain. Ischaemic pain was then induced by inflating the tourniquet to a pressure in excess of systolic arterial pressure and asking the patient to exercise the occluded arm until the ischaemic-induced pain was of equal intensity to their clinical pain. At that point lignocaine  $3 \text{ mg kg}^{-1}$  was administered i.v. over a 3-min period by means of a Harvard pump, followed by an infusion of lignocaine  $4 \text{ mg min}^{-1}$  for a period of 1 h. Arterial blood samples were taken before and immediately following the administration of the 3-mg  $\text{kg}^{-1}$  injection of lignocaine and at 1, 2, 3, 5, 10, 15, 30, 45 and 60 min during the infusion of lignocaine i.v. The scoring of the pain intensity for both clinical and ischaemic pains was undertaken simultaneously with the drawing of each blood sample. The concentration of lignocaine in whole blood was determined subsequently using a gas chromatographic technique as described by Kennaghan (1968).

Two modifications to the plan were required during the course of the study. In two instances the lignocaine infusion was curtailed before the last sampling time when signs of mild toxicity de-

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TABLE I. Individual patient data and doses of lignocaine. Asterisks denote dose attained before mild toxicity symptoms necessitated curtailment of infusion

Patient	Diagnosis	Age (yr)	Weight (kg)	Lignocaine dose (mg)		
				Bolus	Infusion	Total
E.H.	Thalamic pain	68	84	300	240	540
H.S.	Post rhizotomy pain	60	60	250	200*	450
P.D.	Arachnoiditis	37	82	240	240	480
B.F.	Trigeminal neuralgia	37	55	200	240	440
D.S.	Phantom pain	53	41	140	180*	320

veloped. Further, all subjects developed intolerable ischaemic pain 15–30 min into the study which necessitated the release of the cuff before the full occlusion time of 1 h had elapsed. A maximum pain score of 100 was then extrapolated for the ischaemic pain intensity until completion of the study.

## RESULTS

The concentrations of lignocaine in arterial blood for each patient are presented in table II. Peak values of  $5.62 \pm 1.39 \mu\text{g ml}^{-1}$  were observed immediately following injection of the  $3\text{-mg kg}^{-1}$  dose, with a rapid decline during the subsequent infusion. Over this time a plateau concentration was well maintained in each patient with mean values about  $1.5\text{--}2.0 \mu\text{g ml}^{-1}$  although, as noted in table I, two patients did not receive the maximum infusion dose of 240 mg. Both patients began to develop signs of toxicity, such as drowsiness, slurred speech, or tremors, at which point the infusion of lignocaine was discontinued. No patient showed any major toxicity and the only changes noted on e.c.g. monitoring consisted of a mild ( $15\text{--}25 \text{ beat min}^{-1}$ ) increase in heart rate.

The scores of pain intensity for ischaemic and clinical pain are presented in table III. Statistical analyses of these scores using the paired Student's *t*

test, showed no difference between the pre-infusion values but at time 0 (immediately on completion of the initial 3-min administration of lignocaine) the clinical pain was diminished to a value of  $12 \pm 11.6$  as against a significantly lesser decrease ( $36 \pm 30.3$ ,  $P < 0.01$ ) for the ischaemic pain. Further, this mild analgesic action on ischaemic pain could not be sustained and the intensity of the pain continued to increase despite the continued infusion of lignocaine, reaching a maximum of 100 in all patients within 15 min. The cuff was released at this time on three patients and at 30 min for the remaining two. In contrast, the severity of clinical pain remained at a level significantly below that of the control during the entire lignocaine infusion. A statistically significant difference in the intensity of pain existed between the ischaemic pain value and the clinical pain value throughout the entire infusion period.

The relationships between the mean values for intensity of ischaemic pain, clinical pain and the mean arterial lignocaine blood concentrations are shown in figure 1. The initial decline in both ischaemic and clinical pain is correlated with arterial lignocaine concentrations in excess of  $3 \mu\text{g ml}^{-1}$ . As the blood lignocaine concentration decreased below  $3 \mu\text{g ml}^{-1}$ , the severity of ischaemic pain increased,

TABLE II. Individual and mean whole blood lignocaine concentrations taken from arterial samples. In patients H.S. and D.S. the final samples were not drawn as infusions had ceased

Patient	Control	Time (min)									
		0	1	2	3	5	10	15	30	45	60
E.L.	0	7.75	4.21	2.94	2.57	2.04	1.46	1.45	1.36	1.32	1.23
H.S.	0	3.94	3.26	2.70	2.35	2.36	2.31	2.05	2.07	2.18	—
P.D.	0	5.66	4.50	3.20	2.57	2.13	1.86	1.52	1.50	1.54	1.54
B.F.	0	5.78	2.78	2.45	2.45	2.52	2.21	2.17	2.08	2.03	2.01
D.S.	0	4.98	4.90	3.29	3.05	2.61	1.58	1.71	1.85	3.82	—
Mean		5.62	3.93	2.91	2.59	2.33	1.88	1.78	1.77	2.17	1.59
SD		1.39	0.88	0.34	0.26	0.24	0.37	0.31	0.32	0.98	0.39

## ANALGESIC

TABLE III. Lineal infusion/beginning all infusion intervals

Patient	Control
Ischaemic pain score	
E.C.	1
H.S.	1
P.D.	1
B.F.	1
D.S.	1
Mean	
SD	
Clinical pain score	
E.L.	1
H.S.	1
P.D.	1
B.F.	1
D.S.	1
Mean	
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31

Fig. 1  
mean  
Follow  
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 $2 \mu\text{g ml}^{-1}$

TABLE III. Linear analogue pain scores for both ischaemic and clinical pain in each patient. Control = pre-infusion values, 0 = end of the rapid infusion/beginning slow infusion period and times thereafter are minutes of steady infusion time. Differences in pain intensity were significant at all infusion intervals although the ischaemic pain scores were extrapolated at a 100 value if the preceding two recordings were at that value. P values from paired Student's *t* test

Patient	Control	Time (min)										
		0	1	2	3	5	10	15	30	45	60	
<b>Ischaemic pain scores</b>												
E.C.	100	70	70	70	70	100	100	100	100	100	100	100
H.S.	80	0	0	0	100	100	100	100	100	100	100	100
P.D.	70	65	70	70	40	90	100	100	100	100	100	100
B.F.	50	25	25	50	75	80	100	100	100	100	100	100
D.S.	25	20	0	75	80	80	90	100	100	100	100	100
Mean	65	36	33	53	73	90	98	100	100	100	100	100
SD	28.72	30.29	35.25	31.14	21.68	10.00	4.47	0	0	0	0	0
<b>Clinical pain scores</b>												
E.L.	50	30	30	30	30	30	10	10	5	5	5	5
H.S.	100	0	0	0	0	0	0	0	0	0	0	0
P.D.	60	20	0	0	20	70	50	20	55	30	0	0
B.F.	50	10	10	10	10	10	2	5	2	2	5	5
D.S.	27	0	0	0	0	0	0	0	1	0	0	0
Mean	57.4	12	8	8	12	22	12.4	7	12.6	7.4	2	2
SD	26.72	11.66	13.04	13.04	13.04	29.50	21.42	8.37	23.78	12.80	2.74	2.74
P	<0.3	<0.01	<0.05	<0.01	<0.002	<0.0005	<0.0005	<0.0005	<0.0005	<0.0005	<0.0005	<0.0005

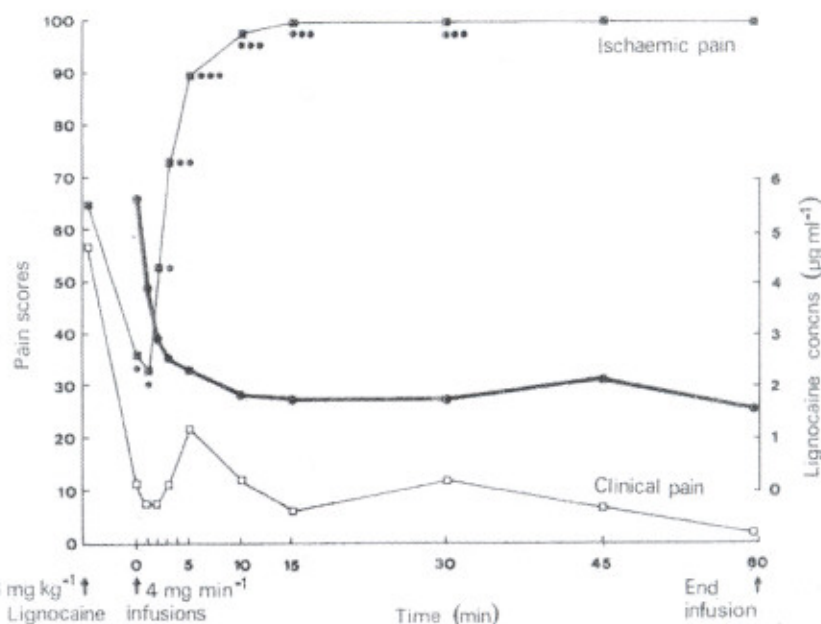


FIG. 1. The effect of lignocaine on clinical (open squares) and experimental pain (closed squares). Graphed mean values are represented for each pain state with mean arterial lignocaine concentrations in the solid line. Following the initial high-dose infusion both pain scores decreased considerably, but the decrease in clinical pain intensity was significantly greater. At a critical concentration of  $3 \mu\text{g ml}^{-1}$ , the analgesic action of lignocaine on experimental pain was lost while that on clinical pain was sustained to values less than  $2 \mu\text{g ml}^{-1}$ . The difference in response was significant ( $P < 0.0005$ ) at 5 min and at each determination thereafter.

mild toxicity

(mg)

Total

540  
450  
480  
440  
320

between the pre-infusion (immediately on completion of the administration of lignocaine) the pain score was reduced to a value of approximately 30. This was significantly lesser decrease than the ischaemic pain. The analgesic action on ischaemic pain was significantly greater and the intensity of the pain was significantly reduced despite the continued presence of a maximum of 100 mmHg cuff pressure. The cuff was released at 30 min for the assessment of the severity of clinical pain, which was significantly below that of the ischaemic pain. A significant difference in the intensity of ischaemic pain value and clinical pain was observed throughout the entire infusion.

In the mean values for clinical pain and the arterial lignocaine concentrations are significantly lower. A significant decline in both ischaemic and clinical pain is correlated with arterial lignocaine concentrations in excess of  $3 \mu\text{g ml}^{-1}$ . As the arterial lignocaine concentration decreased below  $3 \mu\text{g ml}^{-1}$ , ischaemic pain increased,

H.S. and D.S. the final samples

	30	45	60
	1.36	1.32	1.23
	2.07	2.18	—
	1.50	1.54	1.54
	2.08	2.03	2.01
	1.85	3.82	—
	1.77	2.17	1.59
	0.32	0.98	0.39

whereas the severity of clinical pain remained significantly decreased. Two of these five patients showed complete abolition of their pain, two others showed almost complete abolition, whereas one patient showed fluctuation in the intensity of clinical pain. This patient suffered arachnoiditis, having a peripheral nerve injury component to his pain, in distinction to the others who were suffering deafferentation pains.

#### DISCUSSION

The results of this study are in agreement with reports of others examining the analgesic action of systemic local anaesthetic agents. However, two critical distinctions are apparent in delineating this analgesic action. First, a mild general systemic analgesic effect is evident at blood concentrations greater than  $3 \mu\text{g ml}^{-1}$ , while a more specific and profound effect is provided at much lower concentrations in patients with central or deafferentation types of pain. Thus Rowlingson and colleagues (1980), in examining peripheral experimental pain, found lignocaine to be without effect in concentrations up to  $3 \mu\text{g ml}^{-1}$  while the effectiveness of procaine on central neuralgic disorders was found to be dramatic in reports by Graubard, Robertazzi and Peterson (1948) who used prolonged infusions of the drug as a method of pain therapy for these and other patients. The doses chosen for the administration of lignocaine in this study were taken from those of Harrison (1975) who devised similar regimens to attain rapid steady blood concentrations for treating cardiac arrhythmias. Although the doses were not tailored to the individual patient, the methodology was simplified without compromising the subsequent kinetic profiles over the limited time-course of the study.

As a consequence of these results it appears that chronic pain of the deafferentation type may be more responsive to the analgesic action of lignocaine in concentrations of about  $1.5\text{--}2.0 \mu\text{g ml}^{-1}$ , at which concentrations we could not demonstrate any general analgesic action.

Against this hypothesis one could argue that the increasing experimental pain diminished the clinical pain, but the early parallel movement of the two responses in this study favours a common action rather than that of one upon the other. Also the ischaemic pain test (Sternbach et al., 1974), used to measure the intensity of clinical pain, produced no apparent change in the pre-existing pain disorder. Restriction of the access of the drug to the tissues of

the occluded limb could also be stated to bias the response in favour of suppression of the clinical pain, but this was the essential point of Rowlingson's paper (Rowlingson et al., 1980) which showed that at the blood concentrations in question, lignocaine had no suppressive effect on peripherally-induced experimental pain.

While any explanation to account for this response is conjectural, part of the action may be the result of a decrease in the rate of neuronal depolarization as occurs in excitable tissues of the heart, or could be from a selective decrease in high frequency impulse transmission as demonstrated by Condouris (1976). Of greater clinical relevance is a recognition that the response to diagnostic blocks in some instances may be as much a result of the systemic activity of the drug, as of the local nerve blocking effect of lignocaine. Such an action would readily explain the discrepancy between effective analgesia of diagnostic blocks and subsequent failure of permanent nerve interruption (Tasker, Orgon and Hawrylyshyn, 1980). Further clinical applications may derive from the use of lignocaine i.v. to assist in the diagnosis of pain disorders or, additionally, such infusions may provide a rational therapeutic alternative to temporary remission of central pain for some patients.

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#### RESPONSES ANALGESIQUES A LA LIGNOCAINE INTRAVEINEUSE

##### RESUME

L'effet analgésique de la lignocaïne intraveineuse a été étudié chez cinq sujets souffrant de douleurs spontanées d'origine neurologique de diverses étiologies. La réponse a été comparée à celle obtenue sur une douleur ischémique provoquée concurrentement, et initialement de même intensité. Après la perfusion d'une dose élevée de  $3 \text{ mg kg}^{-1}$ , permettant d'atteindre des concentrations de lignocaïne supérieures à  $3 \mu\text{g ml}^{-1}$ , les deux douleurs diminuent et la douleur spontanée davantage que l'autre, ce de façon statistiquement significative. Après cela, à des doses et des concentrations sanguines plus faibles, la lignocaïne est restée sans effet sur la douleur ischémique, alors qu'elle supprimait presque

complètement la douleur spontanée chez le même patient. Les résultats suggèrent une divergence dans la spécificité de l'action analgésique de la lignocaïne i.v. selon la nature du processus causal de la douleur. Les troubles se manifestant comme une déafferentation ou des douleurs neurologiques d'origine centrale semblent affectés favorablement par la lignocaïne i.v., alors que les douleurs d'origine périphérique ne sont pas modifiées par la lignocaïne, sauf à des concentrations sanguines proches des valeurs toxiques.

#### RESPUESTAS ANALGESICAS A LA LIGNOCAINA INTRAVENOSA

##### SUMARIO

Se evaluó el efecto analgésico de la lignocaína intravenosa en cinco pacientes con dolor neurálgico clínico de diversas etiologías. La respuesta se comparó con la del dolor isquémico inducido al mismo tiempo, que al principio fue de la misma intensidad. A raíz de una infusión de alta dosis,  $3 \text{ mg kg}^{-1}$  (las concentraciones de lignocaína fueron superiores a  $3 \mu\text{g ml}^{-1}$ ), ambos dolores clínicos disminuyeron hasta un grado significativo. Con posterioridad y con dosis y concentraciones sanguíneas inferiores, la lignocaína no ejerció efecto alguno en el dolor isquémico, pero suprimió casi totalmente el dolor clínico. Los resultados sugieren que la actividad analgésica de la lignocaína intravenosa es específica, según sea la naturaleza del proceso de inducción del dolor. Los desórdenes que se manifiestan como una diferenciación o neuralgias centrales parecen ser afectados favorablemente por la lignocaína intravenosa, mientras que ésta no afecta al dolor de origen periférico, excepto a concentraciones sanguíneas que se acercan a valores tóxicos.

##### REMARKS

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