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ORIGINAL COMMUNICATION

Propofol analgesia in central pain: preliminary clinical observations

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Abstract Propofol, an intravenous general anaesthetic, has been reported to relieve some forms of pruritus at subhypnotic doses. We assessed its effectiveness in 32 patients with several kinds of non-malignant chronic pain, in a placebo-controlled, double-blind study. We found that central pain, but not neuropathic pain, is at least partially controlled by propofol at subhypnotic doses, without major side-effects. In particular, allodynia associated with central, but no neuropathic, pain has been completely controlled. Propofol analgesia leads to renormalization of brain metabolism as seen on single photon emission computed tomography. We conclude that propofol may help in the diagnosis of central pain, particularly in unclear cases, and also in treatment. Possible mechanisms of action are discussed.

Key words Central pain · Neuropathic pain · Propofol · Single photon emission computed tomography

Introduction

Central pain syndromes represent a major source of suffering, as no uniformly effective treatment is available [9]. Amitriptyline, a tricyclic antidepressant, is the only drug that has been validated by controlled studies of both central and neuropathic pain [19]; unfortunately, it is ineffective in several cases, and may have to be discontinued because of side-effects. Neurosurgical procedures, both ablative and augmentative, are, to a large extent, ineffective [16].

Recently, a Swiss group reported on the effectiveness of propofol, an intravenous general anaesthetic, at subhypnotic doses (15 mg) in the control of pruritus associated with cholestasis and spinal morphine administration [2–4]. Given the close association between pruritus and pain, we administered this drug to treat thalamic pain, for the first time in September 1992 [7] and, thereafter, for different types of central pain and other miscellaneous forms of chronic pain. We assessed the effects using single photon emission computed tomography (SPECT). We describe the clinical effects of propofol on our first 32 patients. Preliminary results have been published previously [6–8, 22].

Table 1 Central pain of cerebral origin

Case Sex Age (years)	CT/MRI findings	Onset of pain	Sensory deficite	Description of pain	Drugs	Pain control by propofol (VAS score reduction)	SPECT
1							
M 39	Small area of left thalamic ischaemia	Sudden (1992)	Thermodolorific hypaesthesia of right hemisoma	Continuous, burning. Allodynia to hand rubbing and hyperpathia to needle	Not tried	4 Allodynia abolished	thalamic hypoperfusion
2							
M 59	Several left cortico-subcortical infarcts, plus left thalamic ischaemia	Gradual (1989)	Thermodolorifio hypaesthesia of right upper limb	Continuous, burning. Shock-like mechanical allodynia (hand rubbing) (glove worn)	Amitriptyline and carbamazepine ineffective	1	Cortical hypoperfusion (increasing under allodynia)
3							
F 56	Right subparietal cavernoma	Sudden (1993)	No gross deficits in left arm (or hemisoma)	Subcontinuous burning plus tingling, then aching (affecting hemisoma during paroxysms). Mechanical allodynia	Amitriptyline ineffective. Carbamazepine: modest effect	4–8 Allodynia abolished	Frontal hypoperfusion
4							
F 63	Left thalamocapsular haemorrhage plus marked subcortical vascular encephalopathy	Subacute (1992)	Previous sensory deficit of right hemisoma, almost completely recovered	Continuous burning (face and leg) and aching (arm). Moderate mechanical allodynia	Amitriptyline ineffective. Carbamazepine: slight effect	1	Severe hemispheric hypoperfusion
5							
M 67	Right thalamic ischaemia	Sudden (1989)	Hypaesthesia of left hemiface, hand and foot	Cold, burning, aching, continuous. Strong allodynia to ice and modest allodynia to hand rubbing (glove worn)	Amitriptyline moderately effective. Carbamazepine ineffective	3–4 Allodynia abolished	Cortical plus thalamic hypoperfusion
6							
M 58	Right thalamocapsular haemorrhage	Sudden (1994)	Moderate thermodolorific hypaesthesia of left trunk, upper arm and thigh	Pins-and-needles in late afternoon. Allodynia to ice in posterior. trunk. No allodynia to needle	Not tried	3–4 Allodynia abolished	Frontal hypoperfusion
7							
F60	Small area of right thalamic ischaemia	Sudden (1992)	Hypaesthesia to touch, pain and heat/cold in left hemitorso and arm	Subcontinuous aching pain plus creeping. Allodynia to ice and needle	Amitriptyline good control	Allodynia abolished	Frontal and thalamic hypoperfusion
8							
M 58	Multiple bilateral ischaemic foci in corona radiata, basal ganglia and right thalamus	Gradual (1991)	No sensory deficits to needle and ice in right foot and hand	Continuous burning (foot; hand only during exacerbations(-allodynia to ice and upon pressing the foot on the floor	Not tried	5 Allodynia abolished	Frontoparietal hypoperfusion

Table 2 Central pain of cora origin

Case Sex Age (years)	Pathology	Onset of pain	Sensory deficits	Description of pain	Drugs	Pain control by propofol (VAS score reduction)	SPECT
1							
M 56	Conocaudal shooting injury	Subacute (1978)	Global hypaesthesia of right leg	Continuous aching (buttock) plus subcontinuous burning discharges (thigh)	Maprotiline: dulls burning; carbamazepine: slight effect	6–10 (aching pain only)	Frontal hypoperfusion
2							
F 66	Postvaccinal paraparesis MRI: negative	Gradual (1990)	No sensory deficits of sacrum and posterior aspects of both legs	Subcontinuous burning plus slight hyperalgesia (needle) to both feet	Carbamazepine: effective control	3–4 Allodynia abolished	Frontal hypoperfusion (right leg stimulus)
3							
M 59	D9 intramedullary cyst	Gradual (1992)	Thermal hypaesthesia on lateral aspects of both legs	Continuous burning plus allodynia to ice and rubbing in left leg	Not tried	6–7 Allodynia abolished	Thalamic hypoperfusion
4							
M 75	C5–6 traumatic discal hernia	Gradual (1993)	Thermodolorific hypaesthesia of both arms	Subcontinuous dysaesthesic pain plus tingling plus polymodal allodynia	Not tried	5–6 Allodynia abolished	Frontal hypoperfusion (left)
5							
F 48	Previous intramedullary D9 cavernoma	Gradual (1992)	Girdle touch-pain hypaesthesia along iliac crests	Continuous burning plus mechanical allodynia (right worse than left)	Not tried	3–4 Allodynia abolished	Frontoparietal hypoperfusion-left
6							
F 78 (deceased)	D8–9 calcific. hernia compressing the cord	Gradual (1987)	Thermodolorific hypaesthesia of left leg, with normal touch and vibratory sensibility	Continuous ripping and burning plus aching paroxysms, no allodynia	Amitriptyline: satisfactory control (initial) carbamazepine: no effect	3–4	Cortical plus thalamic hypoperfusion
7							
F 38	Conocaudal traumatic injury	Gradual (1990)	Touch and thermodolorific hypaesthesia of sacrum and legs	Continuous pushing, burning, crushing, plus paroxysms (also vagina); no allodynia	Amitriptyline and carbamazepine: no effect	4–5 (only in legs)	Not done
8							
M 52	Shunted cervical syringomyelia	Gradual (1993)	Thermodolorific hypaesthesia of torso and left arm	Steady burning plus crushing pain plus electrical shock-like paroxysms mechanical allodynia	Amitriptyline: poor control partial response to lamotrigine	2–3 Allodynia abolished	Frontoparietal hypoperfusion (right)

Table 3 Other chronic pains in which propofol was tested

Type of pain	Number of cases/Sex
Postherpetic neuralgia	3F 1M
Facial pain:	
atypical paroxysmal[a] trigeminal neuropathic: shooting	1M
trauma	1M
post-thermo[b] rhizotomy	1M
post-Fogarty	1F
anaesthesia dolorosa	1F (see case report)
Painful myelinic polyneuropathy	1M
Narrow spinal canal (leg dysaesthesias)	1M
Painful spastic paraparesis	1M
Paroxysmal anorectal pain	1F
Arachnoiditis[c]	1F
Periduritis (failed back surgery syndrome)	
Posttraumatic "crush" painful neuropathy (chest)	1M
Stump (and a lesser phantom) pain	1F

[a] Unresponsive to a trial of motor cortex stimulation
[b] Also unresponsive to 12 h infusion
[c] Partial response to 12 h infusion of buprenorphine, but unresponsive to subarachnoid morphine (1 mg)

Materials and methods

After obtaining written informed consent from the patients and approval from the local ethical commission, we evaluated 32 patients with different kinds of chronic non-neoplastic pain, including 16 with central pain (see Tables 1–3), from September 1992 to July 1994. All patients underwent a comprehensive preliminary cardiological and general neurological examination. Then propofol (Diprivan, Zeneca) was injected as a single intravenous bolus of 0.2 mg/kg. A placebo, a soya bean oil emulsion, with the same colour and consistency (Intralipid, KABI) was administered before or after the propofol test. The patients were advised that the tests performed were to identify drugs which could act on pain, and that the injections could lead to an increase or decrease of pain or no change. Both patients and observers were blind to the injections. Each test was repeated twice. A basal estimation of spontaneous pain was recorded on a visual analog scale (VAS) [24]. Thereafter, injections of propofol or Intralipid were given intravenously. VAS estimations were made every 5 min for 30 min. Noise and variation of luminance were avoided. Allodynia, when found, was also assessed every 5 min together with spontaneous pain. All patients with central pain (except case 7, Table 2), all 4 patients with postherpetic neuralgia, the patient with stump pain and the patient with anaesthesia dolorosa (see case report) were evaluated with SPECT (for details, see ref [7, 8]). Patients who responded to propofol tests and were willing to undergo infusion were infused at 0.3 mg/kg per hour for 6–24 h, under continuous electrocardiogram (ECG) and blood pressure monitoring. Blood parameters were assessed before and after the infusion.

Results

Propofol did not reduce non-central pain, nor did placebo. In all patients with central pain, except for cases 2 and 4 (Table 1) with severe ischaemic encephalopathy, pain was reduced by at least 3 VAS points; in some cases, almost complete relief was achieved (case 3, Table 1; cases 1, 3, 4 and 7, Table 2). In all responders, allodynia was abolished. Placebo was either ineffective or reduced the spontaneous pain by no more than 2 VAS points, but had no effect on allodynia. Propofol analgesia generally lasted no more than 10 min, but in a few cases it lasted up to 20 min, with pain rapidly returning to baseline after this time. In case 7 (Table 1) allodynia was abolished, but not the spontaneous pain.

Infusion in the 2 non-responders proved ineffective. Infusions in cases 5, 7 and 8 (Table 1) lasted 24, 6 and 6 h respectively, and in cases 1, 6, 7 and 8 (Table 2) were given for 6, 12, 12 and 6 h. Better analgesia was always achieved with infusions than with boluses, except in cases 8 (Table 2) and 7 (Table 1). Complete analgesia was seen in case 1 (Table 2; lidocaine infusion controlled paroxysmal pain [20]). In those patients in whom allodynia was much more harassing than steady pain, although the latter was not completely abolished, absence of allodynia allowed patients to resume normal activities during the infusion period (e.g. case 8, Table 1). In all cases, the analgesic effect was maintained for 4–12 h after the infusion, depending on the duration of the infusion (however, see also the case report below, where pain relief persisted 16 h after the infusion).

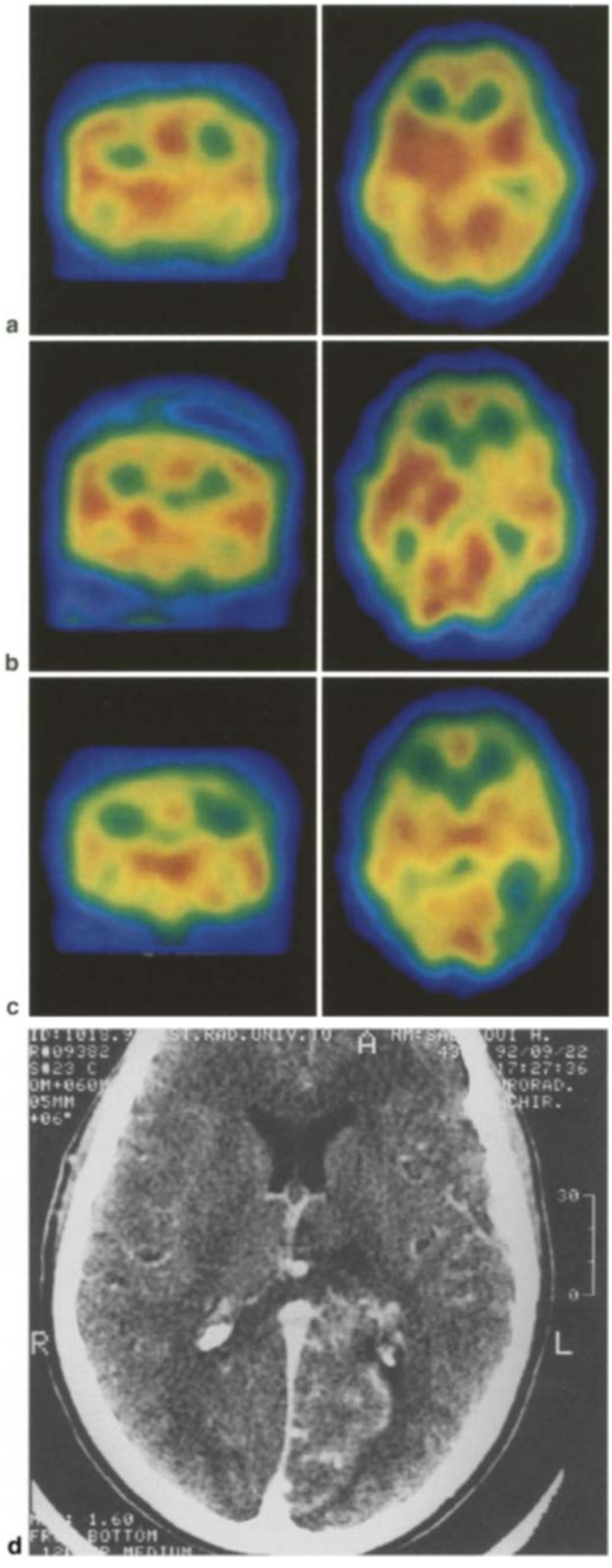
Burning at the site of injection was seen in a few cases for 1–2 min, as were diplopia and dizziness. No ECG, blood pressure or consciousness alterations were ever seen. Blood parameters remained within normal ranges or did not exceed previous values.

Whenever patients had some benefit from propofol, SPECT anomalies were abolished or much reduced (e.g. Fig. 1) (see also [8] and comment).

The patient with the most gratifying pain control was a woman with facial anaesthesia dolorosa (see Table 3), whose case is reported below. She was the only responder among the patients listed in Table 3 (see Discussion).

Case report

This 46-year-old woman developed tic douloureux in 1974. After a trial of carbamazepine, several thermocoagulations resulted in only transient benefit, with pain involving the first and second left trigeminal branches and returning unabated each time. Dandy's operation led to pain relief for about 1 month; then pain slowly re-



emerged, worsened by two more fifth nerve rhizotomies, the last of which left the patient with a sensory deficit also in the left leg and trunk. Years later, a gasserian stimulator was only moderately effective and was later removed. The patient was treated with the full spectrum of analgesic drugs, without avail, except for a certain degree of pain dampening achieved with morphine. On admission in 1992, the patient showed left cheek hypaesthesia with anaesthetic patches. The pain, which was continuous, had a mechanical quality (on pressure), with paroxysms and fluctuations throughout the day under several stress factors (anger, weather changes, etc.). The pain was both superficial and deep, with radiation, along the cheek and to the teeth. Intensity ranged from 2–3 to 10 VAS points. There was mechanical allodynia in response to touch. SPECT showed frontoparietal hypoperfusion (see illustrations in [7]), and MRI disclosed a low temporal cyst, due to previous thermorhizotomies. SPECT findings were later confirmed by positron emission tomography (Lucignani G, Fazio F:S. Raffaele Hospital, Milan, Italy) in 1993. Propofol bolus reduced her pain by more than 50%, whereas placebo was ineffective. The drug was then infused for 12 h, with pain gradually decreasing, reaching 100% control after 1–2 h; analgesia was maintained for 16 h after the infusion. Pain then gradually returned; however, a 24-h infusion again had an analgesic effect, lasting 12 h after the infusion. Return of pain was then controlled by application of a constant-release portable elastomeric infusion pump (2 ml/h), with complete analgesia during a 14-day infusion. This patient will receive propofol through a subcutaneous port communicating with the subclavicular vein. No ECG or pressure alterations were recorded. The patient remained fully alert and responsive, attending to her affairs as before the onset of disease. Blood tests did not exceed preinfusion levels, except for a slight increase in liver transaminases.

Discussion

Propofol (2,6-diisopropylphenol) is an intravenous anaesthetic agent structurally unrelated to other anaesthetic agents; it is strongly hydrophobic. Like barbiturates, it uniformly depresses the metabolic activity of the rat CNS. The thalamus is particularly depressed by propofol, with stronger inhibition than with other anaesthetic agents. Anaesthetic doses of propofol reduce by more than 60% the metabolic activity of the spinal cord central grey mat-

◀ **Fig. 1** SPECT scans of case 1 (Table 1). This patient developed thalamic ischaemia following complete embolization of a left occipital arteriovenous malformation (both shown in the CT scan, **d**), and thereafter central pain. Both basal (above) and stimulation (middle) scans show thalamic hypoperfusion. Propofol bolus reduced the pain and renormalized the SPECT anomaly (below). The left anomalies and CT findings are seen on the right side of the picture

ter, the thalamus (ventrobasal, anterior and lateral nuclei), the somatosensory cerebral cortex, the frontal and cingulate cortex and the presubiculum [10].

Central pain can often be temporarily relieved by subanaesthetic doses of thiopental sodium, but not by the usual doses of opiates [25]. Propofol, administered at 0.2 mg/kg, corresponds to one tenth of the narcotic ED_{95} described for human subjects [23]. As the potency ratio between propofol and thiopental is 1:1.6 [15], it is apparent how the employed dose of propofol is much lower than the dose of thiopental effective in 73% of patients with central pain (136 mg), as described by Tasker [25]. In fact, 15 mg propofol would correspond to 24 mg thiopental, i.e. about 20% of the effective barbiturate dose according to Tasker.

Propofol, like barbiturates and other general anaesthetics, acts on GABA-a receptors, though on a different recognition site from the barbiturates and the benzodiazepines [11, 12], but unlike barbiturates, potentiates glycinergic transmission [17] and may inhibit excitatory glutamatergic conduction [1]. GABA, the most important inhibitory transmitter in the CNS, is widely distributed in the cerebral cortex [13] and in the thalamus: $GABA_a$ receptors are especially well represented in ventroposterolateral-medial thalamic nuclei, but somewhat deficient in the inhibitory thalamic reticular nucleus [18]. Given the ineffectiveness of propofol in chronic non-central type pain syndromes, GABA mechanisms cannot alone explain propofol analgesia. We believe that propofol relieves central pain by interfering with a reverberating (oscillating) thalamocortical generator, marked by thalamocortical flow alterations on SPECT ([5, 7, 8, 8b]; Chen's comment in [8]), which would also explain the efficacy of propofol in our anaesthesia dolorosa patient. Propofol analgesia is accompanied by normalization of SPECT anomalies [7, 8, 22]. The ineffectiveness of propofol in treating postherpetic neuralgia and its allodynia and the absence of SPECT anomalies in this syndrome [8] further support this concept. Low doses of barbiturates are said to abolish the calcium-spike bursting seen in the thalamus and elsewhere in the CNS of central pain patients [26]; however, bursting suppression cannot account for propofol analgesia, as this is also seen in postherpetic neuralgia, where propofol is ineffective [8]. Since GABA transmitters may be either inhibitory or excitatory, depending on the brain region in which GABA transmission is active [14], propofol may actually renormalize neuronal metabolism by direct activation [7].

Whenever there is marked thalamic or cortical anatomical disruption, propofol would be expected to be either ineffective or less than effective; this was seen in our two non-responders (in whom SPECT anomalies did not renormalize after propofol) and other partial responders, with lesser degress of disruption. Supporting our contention, the best results were seen in cord central pain and in the patient with a cavernoma in the corona radiata, but also in the single patient with facial pain who, on the basis of SPECT findings, is surmised to have a central pain-like generator.

Barbiturates have been used to evaluate the effectiveness of neuroaugmentative neurosurgical procedures for central pain [28], with the best responses seen in barbiturate-sensitive patients; they are also used, as discussed, in the diagnosis of central pain [25]. We advocate the use of propofol instead of barbiturates in such diagnostic-prognostic evaluations (pharmacological dissection [27]). Our case 4 (Table 2) a propofol non-responder, was not relieved by a trial of motor cortex stimulation, whereas case 8 (Table 2), a propofol responder, was partially relieved by parietal cortex stimulation, supporting our contention.

In conclusion, propofol has proved effective for transiently controlling central pain, particularly allodynia rather than spontaneous pain. Since evoked pain is often more harrassing than steady pain [21], the effect of propofol is of major interest. Propofol may be used in diagnosis and for short-term control of central pain. The present results and the safety of propofol must be confirmed in larger numbers of patients over longer periods of time, and different doses could also be tried.

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Note added in proof We injected a 60-year-old woman who had central pain and multiple ischemic areas on MRI with propofol. The effect was slight. However, this patient responded dramatically to lamotrigine, an anti-glutamatergic drug, in a dosage of 100 mg b.i.d. PO. This case raises the possibility that central pain may be differentially sustained by selective neurotransmitteer involvement (GABA/glutamate).