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Ultrasound has no anti-inflammatory effect

D. H. GODDARD,[1] P. A. REVELL,[2] J. CASON,[3] S. GALLAGHER,[4] AND H. L. F. CURREY[1]

From the [1]Rheumatology Department, the [2]Department of Morbid Anatomy, the [3]Bone and Joint Research Unit, and the [4]Department of Medical Physics, The London Hospital, London E1

SUMMARY The use of therapeutic ultrasound within the Health Service is widespread and growing. The most common indication is to reduce inflammation. We have tested the influence of ultrasound on a model of acute inflammation in the rat, and we have found a complete absence of any anti-inflammatory action.

Physiotherapy, a valuable service which is in short supply in the Health Service, is labour-intensive and therefore expensive. It is thus important to ensure that it is employed only to provide treatments that are effective.

With this in mind we decided to study the efficacy of therapeutic ultrasound. Claims have been made that ultrasound modifies both the acute and chronic phases of inflammation.[1-3] This has led to the widespread and growing use of ultrasound in physiotherapy practice, with claims that it reduces oedema, relieves pain, encourages healing, and modifies scar formation. However, a review of the reports on which these claims are based makes it clear that there is an urgent need for carefully controlled clinical studies to justify its widespread use by physiotherapists.[4]

Experimental studies have shown that ultrasound enhances protein synthesis by fibroblasts in vitro,[5] but it is difficult to extrapolate this to explain anti-inflammatory effects or resolution of chronic inflammatory lesions. One recent study[6] did attempt to measure the effects of ultrasound on inflammation induced by intracutaneous injection of silver nitrate in the rat, but this study produced discrepant results which depended on the duration and intensity of insonnation.

Our enquiries led us to believe that the indication for most therapeutic ultrasound prescribed within the Health Service is acute inflammation in some form. We have therefore chosen to study the influence of ultrasound on the inflammatory oedema and inflammatory cell infiltration into irritant sponges implanted subcutaneously in the rat. This is a model of acute inflammation which we have previously shown to be markedly sensitive to a range of anti-inflammatory drugs.[7] We have therefore compared the influence of ultrasound with that of a standard nonsteroidal anti-inflammatory drug, flurbiprofen.

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Correspondence to Dr D. H. Goddard, Department of Rheumatology, Westminster Hospital, London SW1.

Materials and methods

Sprague-Dawley rats weighing 250–300 g were used. The preparation, implantation, and processing of polyurethane foam cubes followed the procedure described previously.[7] Each cube, weighing 17 mg, was impregnated with a suspension of heat-killed *Mycobacterium tuberculosis* (approximately 0·3 mg dry organism per cube), and dried and sterilised before implantation. Under ether anaesthesia and through a single dorsal midline incision one cube was implanted subcutaneously into each of the 4 flanks of the rat. Animals were killed on day +4. During removal of the cubes care was taken not to squeeze out any oedema fluid. The cubes were dried to constant weight at 37°C, and the difference between the initial and final dry weights was recorded as a measure of the protein content of the inflammatory exudate. Animals were treated or sham-treated daily from day 0 to day +3 with ultrasound.

A therapeutic ultrasound machine type Rank Stanley Cox Multiphone Mk II was used. The sonic output was carefully calibrated by means of an ultrasound balance to an accuracy of ±5%. The transducer used in these experiments had an effective radiating area of 3·70 cm^2 at 1·5 MHz frequency. The duty cycle of the pulsed beam was 1:1.

The area overlying one hind cube implant was treated. The front cubes therefore served as within-animal controls to detect any systemic effect of ultrasound. A separate control group of rats was treated in an identical fashion, except that this group received dummy insonnation (application of the transducer with the power supply switched off). During insonnation (actual or dummy) the animals were maintained under light ether anaesthesia.

The area to be insonnated was shaved of fur. In preliminary experiments castor oil was used as the coupling medium. Animals that were treated in this way looked sick and lost weight. Moreover, despite careful insonnation, several animals suffered skin burns, which had an obvious systemic effect manifest as a loss of body weight as well as a reduction in the dry weight gain of the cubes. Therefore in all experiments reported in this paper water has been used as the coupling medium. This is also used as the coupling medium in clinical practice.

Animals receiving flurbiprofen were given the drug as a single daily dose of 3 mg per animal suspended in 0·25% carboxymethycellulose. Control animals were given a comparable volume of carboxymethylcellulose alone. The drug was administered via an oral feeding tube from day 0 to day +4.

Cellular exudation into cubes was assessed by the depth of cellular infiltration into each cube measured microscopically with an eyepiece graticule aligned at 10 positions around the periphery of the tubes in 5 μm thick sections stained with haematoxylin and eosin. All measurements were made without knowledge of the treatment allocation. The number of cubes examined in each treatment and control group is shown in Table 3.

Results

Protein content of the fluid exudate. Ultrasound given in a dose range below that which caused the animals to lose body weight had no detectable effect on the dry weight gain of treated sponges (Table 1). This contrasted sharply with the reduction in dry weight gain in the sponges from animals treated daily with flurbiprofen (Table 2), which represents nearly complete suppression of that component of the fluid exudation in the inflammatory response attributable to the irritant tubercle bacilli in the cubes.

Cellular infiltration. Table 3 shows the depth of penetration of inflammatory cells into the sponges. There is no evidence that the sponges from the sonnicated area (right rear) or the other sponges in the treated animals are different from those in the

Table 1 *Dry weight gain (mg: mean ±SD) of sponge cubes treated or sham-treated with ultrasound (transducer applied over back right sponge). Each dosage level represents a separate experiment*

Ultrasound intensity and duration	*Animal numbers*	*Treated*				*Sham-treated*			
		Front		*Back*		*Front*		*Back*	
		Right	*Left*	*Right**	*Left*	*Right*	*Left*	*Right**	*Left*
0·5 watt cm^{-2}	7 T								
for 2·5 min	7 sham	47±6	48±10	52±9	50±8	48±9	47±16	59±8	47±6
1 watt cm^{-2}	13 T								
for 2·5 min	12 sham	53±10	54±16	49±15	43±13	52±11	60±16	57±11	47±11
1 watt cm^{-2}	6 T								
for 5 min	5 sham	67±11	62±13	60±14	58±17	56±7	68±7	57±13	54±9
2 watt cm^{-2}	5 T								
for 5 min	5 sham	49±16	55±14	46±14	51±10	63±6	60±12	58±5	50±3

*Site of application of ultrasound transducer.
T=treated animals.

Table 2 *Dry weight gain (mg: mean ±SD) of sponge cubes from rats treated with flurbiprofen and controls (carboxymethyl cellulose). Also shown, for comparison, are the dry weight gain of nonirritant sponge cubes (non-Tb impregnated) in untreated animals*

Flurbiprofen				*Carboxymethyl cellulose*				*Nonimpregnated sponges in untreated animals*			
Front		*Back*		*Front*		*Back*		*Front*		*Back*	
Right	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*
36±8 (n=4)	36±6 (n=5)	28±7 (n=4)	26±5 (n=5)	73±3 (n=3)	75±5 (n=3)	71±11 (n=4)	59±9 (n=4)	23±2 (n=7)	24±4 (n=7)	23±1 (n=7)	22±2 (n=7)

Table 3 *Depth of cellular infiltration (mm: Mean±SD) of sponge cubes from rats either treated or sham-treated with ultrasonication (dose =2 watts cm^{-2} for 5 min). The ultrasonic transducer was applied over the back right sponge site. For comparison the results are shown also of a separate experiment in which no ultrasonication was administered, but the animals received either flurbiprofen (3 mg) or suspending agent alone daily by mouth*

Ultrasound				*Sham treated*				*No sonication*	
Front		*Back*		*Front*		*Back*		*Flurbiprofen*	*Controls*
Right	*Left*	*Right**	*Left*	*Right*	*Left*	*Right**	*Left*	*All sites†*	*All sites*
0·74 ±0·04 (n=9)	0·70 ±0·06 (n=9)	0·70 ±0·08 (n=8)	0·71 ±0·05 (n=9)	0·76 ±0·08 (n=8)	0·69 ±0·07 (n=10)	0·74 ±0·06 (n=10)	0·76 ±0·07 (n=8)	0·20 ±0·13 (n=10)	0·65 ±0·11 (n=10)

*Site over which ultrasound transducer applied.
†$p<0·001$.

sham-treated control rats. However, the result of the separate experiment in which one group of animals received the drug flurbiprofen illustrates the dramatic effect in this model of a standard nonsteroidal anti-inflammatory drug.

Discussion

We have chosen to test the effect of ultrasound on the acute inflammatory response of rats to subcutaneously implanted irritant sponges. This is a model which has been used extensively in our laboratory. It offers a highly reproducible method of measuring both components of inflammation, namely fluid exudation and cellular infiltration; and the response can be readily suppressed by nonsteroidal anti-inflammatory drugs.[8] By this yardstick, and in striking contrast to a conventional nonsteroidal anti-inflammatory drug (flurbiprofen), ultrasound showed no evidence of any anti-inflammatory activity.

It is difficult to estimate what should be regarded in this animal model as a regimen of ultrasound equivalent to that used therapeutically. Our preliminary experiments suggest that the dosage range we have employed approaches that which will produce toxic effects in the rat. Ultrasound can be delivered in different dosage schemes. The regimen of daily pulsed insonnations employed here was designed to resemble that used clinically in many physiotherapy departments. The distribution of ultrasound energy through the body of a rat is not known. We therefore used an experimental protocol which should have detected both local and distant anti-inflammatory effects.

While it is possible (but not, so far as we are aware, established) that ultrasound has therapeutically desirable effects other than an anti-inflammatory action, it appears likely that this is the main indication for its use at present. In the light of this, our failure to find any evidence of anti-inflammatory action of insonnation in the rat model raises important questions about the widespread and growing use of therapeutic ultrasound in the Health Service.

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