Clenbuterol, a $\beta$-adrenoceptor agonist, increases relative muscle strength in orthopaedic patients

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1. The sympathomimetic agent clenbuterol has a muscle-specific anabolic effect in normal and wasted muscles from animals. This trial was designed to examine the effect of the drug on the recovery of muscle strength and area after open medial meniscectomy.

2. A double-blind, completely randomized, placebo-controlled study was carried out on 20 healthy male patients. Muscle strength and cross-sectional area were determined before and after surgery. Patients were treated with drug or placebo for 4 weeks postoperatively and there was a 2 week washout period.

3. The results suggest that, in the operated leg, clenbuterol treatment is associated with a more rapid rehabilitation of strength in knee extensor muscles; in the unoperated leg, knee extensor strength increased above the initial values after 6 weeks ($P=0.01$). However, in terms of absolute strength the differences were not significant between the two groups.

4. It is concluded that the data lend support to the proposition that clenbuterol has therapeutic potential in the treatment of muscle-wasting conditions.

INTRODUCTION

Muscle represents over half the body mass and is not only involved in movement but also acts as a source of protein which can be called upon in times of disease or adversity. Many disease conditions lead to debilitating, sometimes fatal, loss of muscle, which cannot be readily reversed or prevented. There are few, if any, satisfactory treatments to ameliorate or limit the progression of such muscle-wasting conditions.

In addition to potent effects on bronchospasm, the sympathomimetic agent clenbuterol specifically promotes muscle protein gain [1, 2] and increases muscle fibre size and muscle strength in both normal [3, 4] and pathological [5, 6, 7] muscle. In particular, the ability of the drug to both limit or reverse chronic or acute muscle wasting [5, 6] has led to speculation as to its therapeutic potential.

Indeed, there is controversy as to whether other, less potent, $\beta$-agonists can also affect muscle strength in man [8, 9]. The evidence indicates that salbutamol, inhaled at a therapeutic dose, does not have an ergogenic effect in athletes [8], whereas sustained-release forms may give rise to increases in muscle strength [9]. Clenbuterol is probably the most potent of the so-called anabolic $\beta$-agonists, and data from animal studies suggest that the drug might elicit an anabolic effect in man at doses within the therapeutic range for the treatment of asthma [10].

Hence, the present study was set up to investigate the therapeutic benefits of clenbuterol in a group of healthy young men suffering from muscle wasting and a reduction in strength arising from damage to the medial meniscus.

METHODS

Trial design

The trial was conducted in a double-blind, completely randomized, placebo-controlled fashion under the auspices of a Doctors and Dentists Exemption Certificate, with the approval of the Grampian Region Health Board Ethical Committee, and with the written, informed consent of the patients.

Treatment with drug or placebo began 12 h postoperatively; for the drug group, treatment comprised 20 $\mu$g of clenbuterol (Thomae, Biberach an der Riss, Germany) twice daily for 4 weeks, followed by a 2 week washout period; the same regimen was used for the group taking the placebo, which comprised standard tablet excipients. Postoperatively, patients returned to the clinic weekly, at the same time of day, for the 4 weeks of treatment and finally at the end of the washout period.

Patients

Patients were males between 19 and 40 years of age attending an orthopaedic outpatient clinic for the investigation of medial meniscal injury. They

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were fit and healthy but were not trained athletes and were not taking other medication; their physical details are given in Table 1. At the initial clinic visit measurements of muscle strength and area were made (see below). Twenty patients were entered into the trial after open medial meniscectomy, on a sequential basis, and were allocated, at random, to treatment groups. Patients were discharged 24 h postoperatively.

**Measurements of muscle strength**

The maximum voluntary isometric force exerted by the knee extensor muscles was determined as the maximum force which could be exerted with the knee held at a right angle and the body restrained to prevent any hip movement during contraction of the knee extensors. The technique and apparatus used were similar to those described by Maughan et al. [11]. Muscle strength was measured as the best of at least three attempts to produce a maximum contraction for each leg. Baseline measurements were made preoperatively, and treatment and washout effects were assessed from postoperative activity during the trial.

### Statistical analysis

Changes in absolute terms were calculated for the periods week 0 to week 1, 2, 3, 4 or 6. One-way analysis of variance conducted on these differences enabled a test to be made to see if a significant change had occurred over the period and also to test whether this difference was the same for both drug and placebo groups. Separate analyses were performed for the operated and unoperated legs.

**RESULTS**

**Patients**

There were no significant differences between the groups of patients with respect to age, body weight or duration of injury (Table 1). No patient in either group reported any side effects to the drug regimen used.

**Muscle strength**

**Unoperated leg.** There was no significant difference in baseline values between groups (Table 1). The placebo group showed no significant change in strength throughout the period (Table 2); at the end of 6 weeks the change in strength was $13.8 \pm 40.7$ N (mean $\pm$ SEM), which was not different from zero (Fig. 1). After 2 weeks of treatment, the drug group showed a small increase in strength (Table 2) and by 6 weeks this trend had increased such that the change in strength was $78 \pm 14.6$ N (mean $\pm$ SEM), which was significantly greater than zero ($P = 0.01$). However, between-group comparison showed that at any one point there were no significant differences in strength between the drug and placebo groups.

**Operated leg.** Injury to the knee was associated with a significant reduction in strength compared with the uninjured leg (Table 1). There was a non-significant difference between the initial values of

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### Table 1. Details of the patients in the drug- and placebo-treated groups. The data are expressed as means with SEMs in parentheses. The durations of injury are given as mean values together with the ranges in parentheses.

<table>
<thead>
<tr>
<th></th>
<th>Placebo-treated group</th>
<th>Drug-treated group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=9)</td>
<td>(n=11)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>30.4 (3.6)</td>
<td>31.50 (2.0)</td>
</tr>
<tr>
<td>Body wt. (kg)</td>
<td>80.1 (3.6)</td>
<td>75.6 (3.1)</td>
</tr>
<tr>
<td>Duration of injury (months)</td>
<td>8.3 (1–18)</td>
<td>6.5 (1–24)</td>
</tr>
<tr>
<td>Initial strength (N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unoperated leg</td>
<td>770 (27.5)</td>
<td>760 (34.1)</td>
</tr>
<tr>
<td>Operated leg</td>
<td>650 (51.5)</td>
<td>574 (52.0)</td>
</tr>
</tbody>
</table>

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### Table 2. Strength of the knee extensors in the drug- and placebo-treated groups. The data are expressed as means and SEMs.

<table>
<thead>
<tr>
<th></th>
<th>Placebo-treated group</th>
<th>Drug-treated group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Operated leg</td>
<td>Unoperated leg</td>
</tr>
<tr>
<td></td>
<td>Mean SEM</td>
<td>Mean SEM</td>
</tr>
<tr>
<td>Initial</td>
<td>650 51.5 770 27.5</td>
<td>574 52.0 760 34.1</td>
</tr>
<tr>
<td>Week 1</td>
<td>261 49.8 751 28.8</td>
<td>289 48.1 787 54.2</td>
</tr>
<tr>
<td>Week 2</td>
<td>478 35.9 745 41.7</td>
<td>148 50.4 825 43.7</td>
</tr>
<tr>
<td>Week 3</td>
<td>517 34.4 780 51.5</td>
<td>528 45.0 826 50.7</td>
</tr>
<tr>
<td>Week 4</td>
<td>534 37.9 780 40.2</td>
<td>526 34.2 826 44.2</td>
</tr>
<tr>
<td>Week 6</td>
<td>579 38.9 782 47.6</td>
<td>600 41.8 838 35.8</td>
</tr>
</tbody>
</table>
the two groups, which had arisen despite randomization; thus the drug group started from a lower baseline strength. In both groups, open meniscectomy gave rise to a further, dramatic loss of muscle strength to about 50% of the initial strength (Table 2, Fig. 1).

Postoperative recovery was associated with an increase in strength in both groups (Fig. 1). Strength in the drug group returned to preoperative levels by 3–4 weeks postoperatively, whereas strength in the control group was still significantly different from zero (i.e. indicating the presence of a change from initial values) at 4 weeks postoperatively. However, as for the unoperated leg above, in terms of the absolute means, comparison between groups showed that these effects did not reach significance.

**Muscle cross-sectional area**

Unfortunately, only five of the placebo-treated and seven of the drug-treated patients had scans pre- and post-operatively due to failures of the computed tomography scanner. The results of this study suggest that administration of clenbuterol to healthy young men recovering from medial meniscectomy may lead to a more rapid rate of rehabilitation in the operated leg, and possibly to a slight increase in voluntary muscle strength in the normal leg. Although there were no significant differences between the groups, the unoperated legs from the control group did not show any significant change from zero during the trial, which would tend to suggest that the results observed in the drug group reflect a drug-related effect and have not arisen from repeated testing or training.

The magnitude of the observed increase in strength in the unoperated limbs is comparable with that observed in healthy muscle from patients treated with salbutamol [9]. However, in contrast, the increase in strength was maintained throughout the 2 week washout period. This may relate to differences in pharmacokinetics and potencies between the two compounds. Comparable data from animals are controversial since, in mice, immobilized muscles have shown a small anabolic response after treatment with clenbuterol [6], although anabolism is not apparent in rats [12, 13]. Thus it is not perhaps surprising that the changes in strength are small and only apparent when considered against zero change. Future studies should focus on denervation [5, 12] or cachexia [7] in which the drug produces larger effects in animals.

Although there was an initial, unexplained and persistent differences in area between the unoperated legs of placebo and drug-treated groups selected at random, no significant change in muscle cross-sectional area was observed in the unoperated or operated legs in either group. This result is in contrast to measurements of muscle fibre hypertrophy in animals [5]. While the basis for this contrast is not clear, there are possible explanations. First, data from animals have either been obtained directly from whole muscles or from individual muscle fibres; thus it is difficult to compare animal and human studies. Secondly, although computed tomography gives reasonable muscle definition, it is possible that the resolution was insufficient to detect small changes in area.

The mechanism of action of clenbuterol under
these circumstances is not known. Protein kinetic studies in animals would suggest that drug action was mediated through short-term changes in protein synthesis [14] and longer-term changes in protein degradation [1, 13]. The effect of clenbuterol on protein turnover in man is the subject of another study. However, in addition to protein metabolic effects, β-adrenoceptor agonists are known to alter muscle excitability [15] and it is proposed that clenbuterol may be mimicking an endogenous nerve-derived myotrophic factor [5]; thus small apparent changes in strength may arise from alterations in recruitment pattern and/or motor neuron firing rate. Alternatively, effects on muscle strength may arise through some facilitation of calcium release [15]. Finally, clenbuterol has an antidepressant action through activation of central adrenoceptors [16]; thus a centrally mediated drug effect such as analgesia cannot be ruled out. Since there were no differences between the groups during the early stages of recovery, this possibility is not considered likely. Hence it is probable that the small increases in strength are due to some muscle-specific action of the drug, the mechanistic basis of which has yet to be elucidated fully.

The results of this study provide further evidence of the therapeutic potential of β-adrenoceptor agonists in the amelioration of muscle-wasting conditions in man. The more rapid rehabilitation of the treated groups of patients suggests that treatment with β-adrenoceptor agonists may provide a safe and cost effective therapy for a range of clinical conditions.

ACKNOWLEDGMENTS

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REFERENCES