depression in rats; this did not occur with nalorphine, bremazocine and cyclazocine. Furthermore, in contrast to morphine and EK, these agents had poor efficacy in the rat tail flick test and in inhibiting gastrointestinal transit (unpublished results; Green 1959).

Against this background, we have recently learned that EK does not substitute for morphine in rats receiving an i.p. infusion of morphine (Teiger 1974) (Dr M. E. Feigenson, Sterling-Winthrop, personal communication).

Taken together, these data show that the in vivo pharmacological profile of EK, in rats, resembles that of morphine far more than the profiles of other proposed κ compounds such as nalorphine, bremazocine and cyclazocine. The major difference between morphine and EK is the lack of substitution by EK for morphine in Teiger's rat model.

In summary, we call attention to the separation between cross-tolerance and cross-dependence in the rat and pose the following question: what criteria should be used to classify opioids in this species?

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Muscle fibrosis associated with intramuscular chlorpromazine administration. A preliminary report

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Muscle damage including fibrosis and contracture has been reported as a complication of intramuscular drug administration (Todd 1961; Gray 1967; Hagen 1968; Norman et al 1970; Stark 1970; Mastaglia et al 1971; Aberfeld et al 1968; Steiner et al 1973; Serrano & Wilder 1974). Psychiatric patients frequently receive antipsychotic medication by intramuscular injection. We report a preliminary study of muscle specimens taken from rabbits given intramuscular chlorpromazine and pentazocine showing muscle necrosis and fibrosis, and we compare these findings with the results of pentazocine injection into human muscle.

Methods

Animal study. Twelve New Zealand white rabbits were given daily intramuscular injections in the antero-lateral quadrant of each thigh according to the protocol described below. Injections were given with chlorpromazine (25 mg cc^{-1} solution, Thorazine, Smith-Kline & French Labs), the buffer solution for chlorpromazine (each cc contained ascorbic acid 2 mg, sodium bisulphite 1 mg, sodium sulphite 1 mg, and sodium chloride 6 mg; pH = 4·7), or pentazocine (30 mg cc^{-1} solution, Talwin, Winthrop). Injected doses of chlorpromazine and pentazocine, comparable to human therapeutic doses, were used: 4·3 mg kg^{-1} dose equivalent to 300 mg/70 kg and 1·4 mg kg^{-1} dose equivalent to 100 mg kg^{-1}. Four rabbit thighs were injected with chlorpromazine 4·3 mg kg^{-1} daily for seven days, four thighs were injected with chlorpromazine 1·4 mg kg^{-1} daily for seven days, and four thighs were injected with buffer solution daily for seven days. On day 8 these six rabbits were killed and muscle specimens from the 12 thighs removed for study. Four rabbit thighs were injected with chlorpromazine 1·4 mg kg^{-1} daily for seven days, four thighs were injected with chlorpromazine 4·3 mg kg^{-1} daily for seven days, and four thighs were injected with pentazocine 1·4 mg kg^{-1} daily for seven days. Fourteen days of healing after the last intramuscular injection was allowed before these six rabbits were killed, and muscle from the 12 thighs removed.

At the time of death, the area of the needle injections in each thigh was identified and the skin was removed by dissection to reveal the vastus lateralis muscle underlying the injection site. The muscle was then dissected free and specimens of muscle taken from the injection site were quick-frozen according to standard techniques of Dubowitz & Brooke (1973). Serial sections were stained with a standard histochemical battery (Dubowitz & Brooke 1973).

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Case report. A biopsy specimen was obtained from the left quadriceps muscle of a 61 year old male physician who reported having injected pentazocine into multiple sites in his anterior and lateral thighs, gluteal areas, and upper arms for at least two years. He had administered over 100 doses of pentazocine to himself during the 6 to 9 months preceding his evaluation. During the second year of these pentazocine injections, he noticed slowly increasing pain and stiffness in his muscles. At the time of the evaluation his gait was stooped and waddling and he had limited motion about the knee, elbow, and shoulder joints. After three days in the hospital with no injections his serum creatine phosphokinase (CPK) was 250 U litre^{-1} (normal less than 180 U litre^{-1}). A muscle biopsy specimen was also obtained on the third day and processed in a manner similar to that described above for the animal specimens. An electromyogram of proximal right arm and leg muscles showed scattered fibrillation potentials and the typically myopathic features of brief, small, abundant motor-unit action potentials.

Results

Animal biopsy specimens (Fig. 1). Gross examination of quadriceps muscle obtained on the eighth day following seven days of single daily chlorpromazine injections (of either dosage) showed numerous areas of purplish discoloration, and the muscle was hard to palpation in comparison with other leg muscles. Histologic sections showed marked muscle fibre necrosis and inflammatory cell infiltration with occasional microhaemorrhagic areas. Quadriceps muscles obtained from animals that were allowed 14 days of recovery following seven single daily chlorpromazine injections were grossly grey-white in appearance and hard to palpation compared with other leg muscles. Histological sections revealed muscle fibres undergoing necrosis and phagocytosis, other regenerating fibres, and wide-spread fibrosis; granuloma formation was also evident. Muscle specimens, removed on the eighth day, from animals that had received only intramuscular buffer, revealed no grossly observable changes and the muscle was normal to palpation. Histological sections showed minor abnormalities (small rounded muscle fibres with a few scattered inflammatory cells) only along the longitudinal needle tracks, with remaining areas of the biopsies appearing normal. Muscles from animals given pentazocine showed gross and microscopic abnormalities similar to (although less severe than) those seen with chlorpromazine-injected specimens allowed 14 days recovery, but without granuloma formation.

Human biopsy specimen (Fig. 2) The muscle biopsy from the patient with pentazocine abuse showed changes of chronic myopathy, including fibrosis and increased

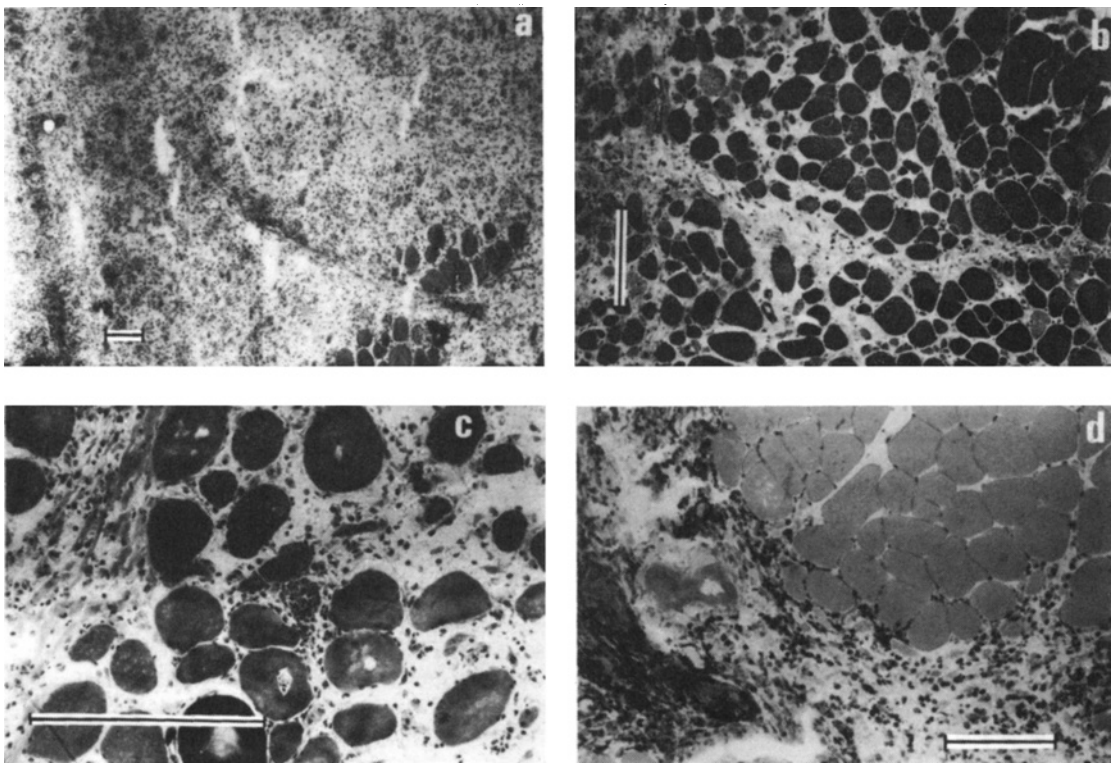

FIG. 1. Rabbit quadriceps muscle specimens (modified Gomori trichrome; scale bar 100 μm); a.b.c. removed after 7 daily injections of chlorpromazine. Note the marked oedema separating muscle fibres, necrosis of muscle fibres, and the fibrosis between fibres. d. removed after 14 days of healing following 7 daily injections of pentazocine.

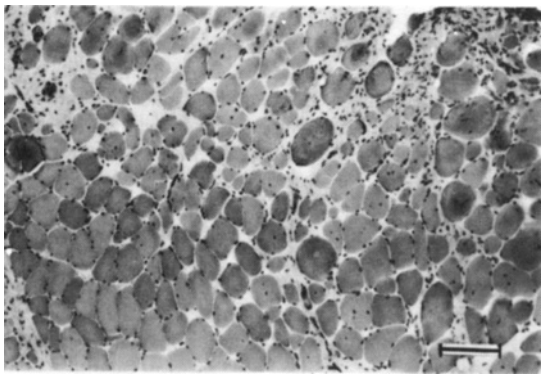

FIG. 2. Left quadriceps muscle biopsy specimen from a patient abusing intramuscular pentazocine showing fibrosis between fibres and variations in fibre size (haematoxylin & eosin; scale bar 100 μm).

amounts of connective tissue separating muscle fibres of varying size. There was no perivascular inflammation. Two isolated degenerating fibres were observed.

Discussion

Our study shows that an animal model demonstrates muscle fibrosis comparable to that found in patients receiving intramuscular medications. The rabbit thigh muscles injected with pentazocine revealed myopathic abnormalities similar to those found in a muscle specimen from a patient abusing intramuscular pentazocine. Intramuscular chlorpromazine injections produced more striking myopathic changes in the rabbit muscle and would be expected to produce similar changes in human muscle.

Although needle trauma alone or with saline injection produces acute necrotic damage of a few muscle fibres with histological appearance of a 'needle track' (Engel 1967), there is subsequent recovery without fibrosis. Our injection of the buffer solution for chlorpromazine produced similar changes. O'Connor (1980) described a patient who had received 200 mg chlorpromazine injections four times a day for 48 h and subsequently developed sterile abscesses in the buttocks, from which fluid containing chlorpromazine was aspirated six weeks later; this muscle damage was attributed to the low pH of chlorpromazine solution used. We doubt that the low pH of the chlorpromazine hydrochloride (pH = 4·7 in our study) contributed significantly to our observed muscle injury, since the buffer solution had the same pH and did not produce similar damage. We therefore assume that the drug compounds themselves must play a role in the genesis of the marked tissue destruction observed in our study.

McCreadie et al (1979) and Starmark et al (1980) have reported subcutaneous tissue necrosis and gluteal abscesses in patients receiving intramuscular neuroleptics. Meltzer & Engel (1970) reported that quadriceps muscle biopsies from psychotic patients showed myopathic muscle histology including necrotic fibres undergoing phagocytosis, fibres with internal nuclei and an irregular intermyofibrillar network, and end-stage atrophic fibres. In our rabbits injected with either chlorpromazine or pentazocine, similar (although much more severe) myopathic changes were seen, and thus, we feel that the findings of Meltzer & Engel may be attributable to neuroleptic administration.

We believe that the possibility of irreversible muscle damage must be considered when intramuscular neuroleptic drugs are given to psychiatric patients. Such administration will usually be justified on the basis of clinical necessity, but this may not always be the case.

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