Assessment of the effectiveness of drugs to substitute for morphine in the opiate-dependent rhesus monkey

N.J. CROSSLAND & M.J. TURNBULL

Department of Biology, ICI Ltd., Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire, SK10 4TF

The effectiveness of acute drug administration to suppress opiate withdrawal symptoms has been assessed in 2 morphine-dependent rhesus monkeys (*Macaca mulatta*). Two monkeys (one of each sex) were maintained on morphine by twice daily injections (Mon-Fri) of 3.6 (♀) and 3.3 (♂) mg/kg i.m. at 0900 h and 5.1 (♀) and 4.9 (♂) mg/kg i.m. at 1630 hours. These doses had been established as sufficient to maintain a similar degree of dependence in each monkey. Only one daily injection of 8.7 (♀) and 8.2 (♂) mg/kg was given (1200 h) at the weekends.

The substitution experiments were conducted on the Wednesday of each week. This involved the substitution of the 0900 h morphine injection by the drug under investigation with behavioural observations for 10 min per monkey at 0830, 1030, 1315 and 1600 hours. Several parameters were assessed and the data were recorded on a multiple event counter. They included locomotor activity, grooming, scratching, yawning and tongue chewing, limb biting, vocalization, piloerection and respiratory rate. Brief notes were also taken on any unusual aspects of gross behaviour.

The experiments were conducted on a blind basis, i.e. the observer was unaware of which drug had been administered and thus compared the results with those previously obtained after the normal morphine injection. Opiate support was characerized by the monkey remaining for the most part in a sitting position, but nevertheless remaining alert, together with grooming activity and a low respiratory rate (Table 1). Conversely, biting of the arms, the presence of piloerection and 'neurotic preoccupations' (anal (♀) or oral (♂)) (neuroses—Table 1) together with hyperventilation were seen during opiate abstinence. A sharp increase in the frequency of yawning and tongue chewing was considered to be indicative of the anxiety which preceded the onset of the other withdrawal symptoms.

As can be seen from Table 1, a dose of morphine as low as 1/8 of the normal dose ameliorated the abstinence syndrome to some extent, although with such low doses the support was short lived. By using these lower doses, the other opiates (pethidine, codeine and dextropropoxyphene) could be compared with the

Table 1 Effect of drug substitution on the behaviour of a morphine dependent monkey (♀)

0900 h treatment		*Parameters indicative of*					
		Opiate support		*Anxiety*		*Opiate withdrawal*	
Drug	*Dose* (mg/kg)*	*grooming (1315 h)*	*hypo-ventilation (1315 h)*	*yawning (1030 h)*	*tongue chewing (1315 h)*	*neurosis (1600 h)*	*hyper-ventilation (1600 h)*
Saline	–	–	–	+++	+++	+++	+++
Morphine HCl	3.6	+++	+	–	–	–	–
,,	1.8	++	+	–	–	+	–
,,	0.9	–	–	–	–	–	–
,,	0.6	–	+	–	–	–	–
,,	0.46	+	–	++	++	+	+
,,	0.36	–	–	–	+++	++	++
Pethidine HCl	6.5	–	+	–	–	–	–
Codeine phosphate	9.6	++	–	–	++	++	++
(+)-Propoxyphene HCl	14.7	–	+	–	–	–	+
Chlordiazepoxide HCl	1.76	–	–	–	+	+	+
Diazepam	0.5	–	–	–	–	–	++
Propranolol HCl	4.3	–	–	+	+	++	+
Chlorpromazine HCl	0.89	–	–	–	–	–	+
Viloxazine HCl	21.7	–	–	+	+++	+++	++

\+ Indicates presence of parameter (+++ = maximum; + = minimum frequency/duration/extent).
– Indicates absence of parameter.
* Dose calculated as base of the salts indicated in the first column.

dose of morphine that gave approximately the same degree of support. Thus codeine 9.6 mg/kg gave very little support and was approximately equivalent to 0.46 mg/kg morphine.

Non-opiate drugs were able to attenuate the abstinence syndrome to a varying degree, but by consideration of the total behavioural pattern, these drugs could be distinguished from opiates.

Full details of the results (which are only summarized in Table 1)—including the time course of appearance of the various parameters measured—will be presented at this demonstration.

A simple device for measurement of respiratory rate in the mouse

N.J. CROSSLAND, G.B. HORSFALL, SALLY T. OXENHAM, J.S. SHAW & M.J. TURNBULL

Department of Biology, ICI Ltd., Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire, SK10 4TF

This technique allows a rapid and accurate measurement of respiratory rate in the mouse. The animal's snout is held into the barrel of a 5 ml plastic syringe cut to a length of 2 cm. A bead thermistor, heated to ≏10°C above ambient temperature, is fitted into the luer inlet/outlet of the syringe thus sensing change in temperature due to breathing (see Figure 1). The electronic unit contains circuitry which shapes and filters the signal derived from the thermistor to produce an on/off cycle for each respiratory cycle. This operation is independent of rate and depth of respiration. The operation of this circuitry is signalled by a flashing indicator. Pressing the 'start' button then initiates the digital part of the circuit. After this initiation, the first signal from the thermistor starts, and the eleventh stops, a counter which is clocked by 10 ms pulses derived from the a.c. mains. On the eleventh count, a digital display illuminates and reads, actually the number of clock pulses received in ten respiratory cycles but, effectively, the mean respiratory interval in milliseconds. This reading remains displayed until the next measurement is initiated by again pressing the 'start' button. An

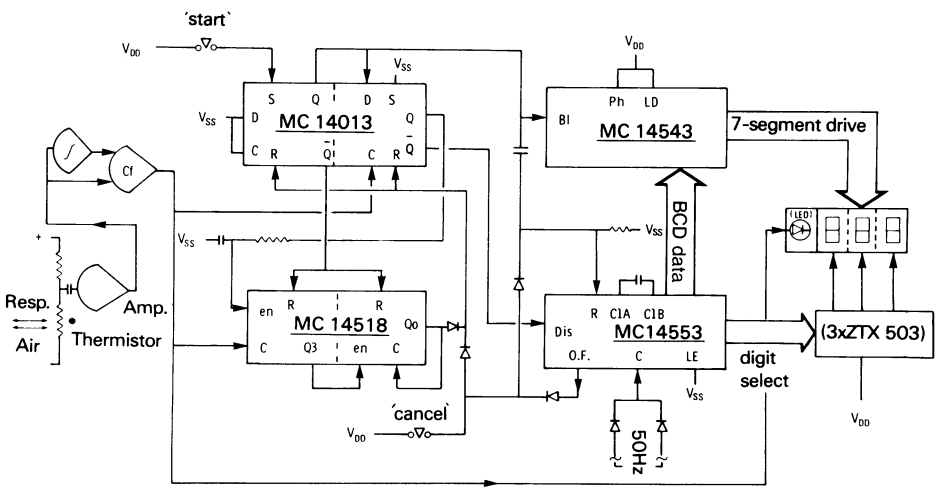

Figure 1 Circuit diagram for measurement of respiratory interval in mice. Motorola CMOS Integrated Circuits: MC 14013, dual D type flip-flop; MC 14518, dual BCD counter; MC 14543, BCD-seven segment driver; MC 14553, 3-digit BCD counter.