Cochlear Toxicity of Butikacin (UK-18,892), a New Semisynthetic Aminoglycoside Antibiotic, in Guinea Pigs

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The cochleotoxic potential of butikacin (UK-18,892), a new semisynthetic aminoglycoside, has been evaluated in neonatal guinea pigs in comparison with amikacin, gentamicin, and kanamycin A. All compounds produced a dose-related increase of the mean threshold sound intensity required to elicit Preyer's reflex. Butikacin produced a similar level of cochlear toxicity to that of kanamycin A, but tended to be less cochleotoxic than amikacin. Gentamicin was the least cochleotoxic.

Aminoglycoside antibiotics are known to cause ototoxicity as a side effect (1, 2, 6). Some (e.g., kanamycin and amikacin) are toxic to the cochlea (3, 4, 7), whereas others (e.g., streptomycin and gentamicin) exert a greater toxic effect on the vestibular system (5, 10). Recently a new neonatal guinea pig system has been described which provides a reliable and valid assessment of the relative cochleotoxic potentials of aminoglycosides (J. R. C. Baird and A. J. Carter, Abstr. Br. J. Pharmacol., 63:410P, 1978; A. J. Carter, manuscript in preparation).

Butikacin, 1-N[(S)-4-amino-2-hydroxybutyl]kanamycin A (UK-18,892), is a new semisynthetic aminoglycoside antibiotic, with a potency and breadth of spectrum similar to that of amikacin (8). This compound has been evaluated for cochlear toxicity in neonatal guinea pigs, in comparison with amikacin, gentamicin, and kanamycin A.

MATERIALS AND METHODS

Redfern strain (Pfizer colony) albino guinea pigs were used. They were taken within 48 h of birth, sexed, weighed, ear-tagged, and assigned to groups of five to six animals. When not engaged in the screening procedure, animals were housed with their respective sows.

Auditory function. The apparatus used consisted of a Levell R.C. oscillator (type T.G. 200; Levell Electronics Ltd., Barnet, Hertfordshire, England), which delivered a pure sine-wave signal of adjustable frequency to a 15-W amplifier/control unit designed and constructed in our instrument laboratory. The sound stimulus was presented by a Goodmans Magnum K2 speaker system in pulses of 0.2 s duration at 1-s intervals.

The threshold sound intensity (dB re 0.0002 dyne/cm² at 30 cm) for Preyer's reflex was measured by positioning each animal, with light manual restraint, with its ears 30 cm from the speaker. The oscillator was set at 2 kHz, and the volume was adjusted to elicit Preyer's pinna reflex. The volume was then reduced until all pinna movement ceased. The volume setting at which this occurred was converted to decibels by means of a calibration chart and taken as the threshold sound intensity. This process was repeated at frequencies of 4, 8, 12 and 16 kHz. The guinea pigs were weighed and auditory function was measured just before dosing each day for up to 40 days, unless either death had occurred or Preyer's reflex had completely disappeared. Deafness was taken as the absence of the reflex at the maximum volume setting available on the apparatus for each frequency used. All experiments were carried out in a soundproof room.

As changes in threshold sound intensity for Preyer's reflex followed a similar pattern at all five frequencies used, daily measurements are presented at 12 kHz only, as this frequency, although not the most sensitive, was considered most representative. Also, for clarity, threshold changes at 12 kHz have been plotted at 2-day intervals. Threshold shifts at all five frequencies after various periods of treatment are also shown. However, as control results were similar in all cases, they are only presented once.

Drugs. Solutions of butikacin sulfate (UK-18,892), amikacin (Biklin, Bristol-Myers Roussel, Swindon, England), kanamycin A sulfate (Pierre), and gentamicin sulfate (Roussel) were prepared in 0.9% saline. Doses contained in a volume of 0.05 to 0.2 ml per 100 g of body weight were administered subcutaneously. The control group received 0.1 ml of saline per 100 g of body weight. All dose levels reported are in terms of base and were selected to reflect the relative antibacterial potencies of the compounds, with butikacin, amikacin, and kanamycin A having broadly similar potencies, all approximately one-third that of gentamicin. Thus, butikacin, amikacin, and kanamycin A were administered at dose levels of 50, 100, or 200 mg/kg per day, and gentamicin was administered at dose levels of 16.7, 33.3, or 66.6 mg/kg per day.

RESULTS

Gentamicin (16.7 mg/kg per day), butikacin, amikacin, or kanamycin A (50 mg/kg per day) were administered for up to 40 days. At these dose levels none of the antibiotics had any effect.
on Preyer's reflex for the first 25 to 30 days of treatment, after which time the mean threshold sound intensities began to rise slowly in all drug-treated groups (Fig. 1). All compounds had a greater effect on the response to higher frequencies (Fig. 2).

When the four antibiotics were administered for up to 40 days at either 100 mg/kg per day (butikacin, amikacin, and kanamycin A) or 33.3 mg/kg per day (gentamicin), there was a greater differentiation. Although thresholds at 12 kHz began to rise between days 12 and 15, complete loss of Preyer's reflex at this frequency required treatment for 23 days with amikacin, 33 days with butikacin, and 40 days with kanamycin A. In contrast, only one animal in the gentamicin group had complete loss of Preyer's reflex at 12 kHz within the 40 days of the experiment (Fig. 3). After 30 days of treatment, amikacin had produced the largest threshold shift, followed by butikacin and kanamycin A; gentamicin produced the smallest change (Fig. 4). As at the lower dose levels, the higher frequencies tended to be affected most.

At the highest dose levels studied (200 mg of butikacin, amikacin, and kanamycin A per kg per day or 66.6 mg of gentamicin per kg per day), all compounds produced similar responses, with rapid loss of Preyer's reflex at 12 kHz occurring within 17 days (Fig. 5). However, after 10 days of treatment, there was a greater threshold shift for kanamycin A and amikacin than for butikacin or gentamicin (Fig. 6).

**DISCUSSION**

The ototoxic potential of butikacin has been compared with that of amikacin, kanamycin A, and gentamicin in neonatal guinea pigs, each compound being tested at three dose levels for...
FIG. 3. Effects of butikacin, amikacin, kanamycin A, and gentamicin on the mean threshold sound intensity (± standard error of the mean) for Preyer's reflex at 12 kHz in neonatal guinea pigs. Symbols: □, control (n = 5); ●, butikacin (100 mg [base]/kg per day s.c.) (n = 5); ○, amikacin (100 mg [base]/kg per day s.c.) (n = 6); Δ, kanamycin A (100 mg [base]/kg per day s.c.) (n = 5); ▲, gentamicin (33.3 mg [base]/kg per day s.c.) (n = 6).

FIG. 4. Change in mean threshold sound intensity (± standard error of the mean) for Preyer's reflex in neonatal guinea pigs after 30 days of treatment. Control results as in Fig. 6. Symbols: ●, butikacin (100 mg [base]/kg per day s.c.) (n = 5); ○, amikacin (100 mg [base]/kg per day s.c.) (n = 6); Δ, kanamycin A (100 mg [base]/kg per day s.c.) (n = 5); ▲, gentamicin (33.3 mg [base]/kg per day s.c.) (n = 6).

up to 40 days. All four aminoglycosides produced dose-related hearing loss, as measured by the change in threshold sound intensity for Preyer's reflex.

Butikacin was consistently less cochleotoxic than amikacin. At the 200 mg/kg per day dose level, for example, there was a difference of three days in the time required to produce complete loss of Preyer's reflex at 12 kHz. Furthermore, after 10 days of treatment, the mean threshold shifts at all frequencies were greater in the amikacin-treated group. At the 100 mg/kg per day dose level, the difference between the two compounds in the duration of treatment required for loss of Preyer's reflex at 12 kHz was 10 days and the threshold shifts were again more marked after amikacin. Comparison of the two compounds at 50 mg/kg per day was difficult, as changes in threshold sound intensities were small. However, there was some indication of a slightly greater effect with amikacin, especially at the highest frequency used.

Kanamycin A tended to fall between the two, being like amikacin at the 200 mg/kg per day dose level and like butikacin at the 100 mg/kg per day dose level. However, it had less effect than either amikacin or butikacin at the lowest dose level. Gentamicin, which was studied at dose levels reflecting its greater antibacterial potency, was the least cochleotoxic, which is consistent with its known more marked effect on the vestibular system (10).

Amikacin and kanamycin A have been shown by other workers to produce similar levels of ototoxicity in animals (7), which is consistent with the results of the present study. This is further borne out by the incidence of ototoxic side effects found in patients treated with amikacin and kanamycin A (9). It is considered that butikacin will probably have an ototoxic poten-
FIG. 5. Effects of butikacin, amikacin, kanamycin A, and gentamicin on the mean threshold sound intensity (± standard error of the mean) for Preyer's reflex at 12 kHz in neonatal guinea pigs. In all groups n = 5. Symbols: □, control; ○, butikacin (200 mg [base]/kg per day s.c.); ◊, amikacin (200 mg [base]/kg per day s.c.); Δ, kanamycin A (200 mg [base]/kg per day s.c.); ▲, gentamicin (66.6 mg [base]/kg per day s.c.).

FIG. 6. Change in mean threshold sound intensity (± standard error of the mean) for Preyer's reflex in neonatal guinea pigs after 10 days of treatment. In all groups n = 5. Symbols: □, controls; ○, butikacin (200 mg [base]/kg per day s.c.); ◊, amikacin (200 mg [base]/kg per day s.c.); Δ, kanamycin A (200 mg [base]/kg per day s.c.); ▲, gentamicin (66.6 mg [base]/kg per day s.c.).

Potential in humans similar to, or slightly lower than, that of amikacin.

LITERATURE CITED