ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 1986, p. 543–548
0066-4804/86/040543-06$02.00/0

Vol. 29, No. 4

MINIREVIEW

Aminoglycoside Research 1975–1985: Prospects for Development of Improved Agents

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INTRODUCTION

Following the synthesis of amikacin and the discovery of its unique properties in 1972 (16, 36), there were high expectations that even more potent and broader-spectrum aminoglycosides (AGs) could be synthesized or identified in soil-organism screens. Consequently, existing research programs were scaled up, and some new ones were initiated. Such efforts were surely justified, because AGs had proven over the preceding decade to be the principal weapon in the armamentarium available for the treatment of seriously ill patients. This key role evolved because, as a class, AGs possess many of the properties considered by infectious disease specialists to be inherently associated with an ideal antibacterial agent. Prominent among their desirable characteristics are (i) potent activity against gram-negative bacilli, (ii) inhibitory action that is relatively unaffected by a large bacterial inoculum, (iii) rapid and essentially complete bactericidal activity, (iv) predictable and dose-proportionate pharmacokinetics, and (v) ability to interact synergistically with beta-lactam and other cell-wall-active antibiotics.

If these were the only properties possessed by AGs, the extent of their usage might have been even greater than has been the case. Unfortunately, all of them also possess the following characteristics: (i) weak activity against gram-positive organisms, (ii) little or no activity against isolates the produce certain AG-modifying enzymes or that have an AG transport system that is impaired or absent, and (iii) an inherent potential to cause ototoxicity or nephrotoxicity, usually in a small percentage of those patients considered to be at risk due to suboptimal renal function. Nevertheless, because this potential has reduced the extent of AG usage, researchers have given high priority to finding safer members of the class.

In this minireview, the results of the last 10 years of AG research are reviewed to ascertain whether there is a likelihood that superior AG derivatives will reach the marketplace and to consider the extent to which AG antibiotics will be used in the future.

(Part of this work was presented at the 25th Interscience Conference on Antimicrobial Agents and Chemotherapy, Minneapolis, Minn., 29 September to 2 October 1985.)

CRITERIA FOR COMPARISON OF AGs

In view of the great importance given to the relative activity of marketed AGs against *Pseudomonas aeruginosa*, potency against members of this species was chosen as the parameter best reflecting overall antibacterial activity. MICs for 50% of strains tested (MIC_{50}s) for wild-type *P. aeruginosa*, determined in plate-dilution susceptibility tests with Mueller-Hinton medium, were used to estimate relative potencies. The MIC_{50} of the gentamicin C complex (gentamicin C) was arbitrarily assigned a value of 1.0, and potency values of all other AGs were calculated on the basis of their activity relative to this standard.

Another important measure of the relative effectiveness of marketed AGs is the degree of their susceptibility to the modifying action of microbially produced enzymes. The comparative response of each of the AGs to the 10 most fully characterized enzymes was considered in this evaluation. Enzymes included the AG phosphotransferases APH (3′)-I, APH (3′)-II, and APH (2″); the adenylyltransferases AAD (4′) and AAD (2″); and the acetyltransferases AAC (2′), AAC (6′), AAC (3)-I, AAC (3)-II, and AAC (3)-III. An AG was considered susceptible to the action of an enzyme only when the mean MIC_{50} of producing strains was at least eightfold higher than that of wild-type strains.

The third and certainly equally important parameter used to compare agents was an estimate of their relative potential to cause ototoxicity and nephrotoxicity in humans. Although animal test results were used to make projections regarding the ability of an agent to cause such toxicity, data obtained from conventional high-dose rat nephrotoxicity and guinea pig and cat ototoxicity models were not used. Instead, the acute intravenous (IV) 50% lethal dose (LD_{50}), in mg/kg (body weight) for mice, was used to estimate the potential of each AG to cause undesirable side effects in humans. Evidence that such LD_{50}s may be reliable indicators of toxicity potential in humans is shown in Fig. 1.

The data plot in Fig. 1 shows that maximum daily doses of AGs approved by regulatory authorities (34; personal communication, N. Chiba, Bristol-Myers Research Institute, Tokyo, Japan [1985]) have a nearly linear relationship with acute LD_{50}s for mice (Table 1). Although it would be desirable to have more data points to unequivocally confirm that a true correlation exists, information on additional compounds is not available. However, it can be clearly seen that there is a cluster of high-mouse-toxicity, low-human-dose points widely separated from several low-mouse-toxicity, high-human-dose points. Because deaths in the LD_{50} tests are almost certainly attributable to neuromuscular blockade, there is no readily available explanation for the observed relationship. Nevertheless, it is patently clear from data presented in the following section that if other researchers had used acute toxicity values rather than results from the more classic animal models to predict human ototoxicity and nephrotoxicity, there would have been many fewer cases in which compounds actually reached the clinical evaluation stage before being abandoned.

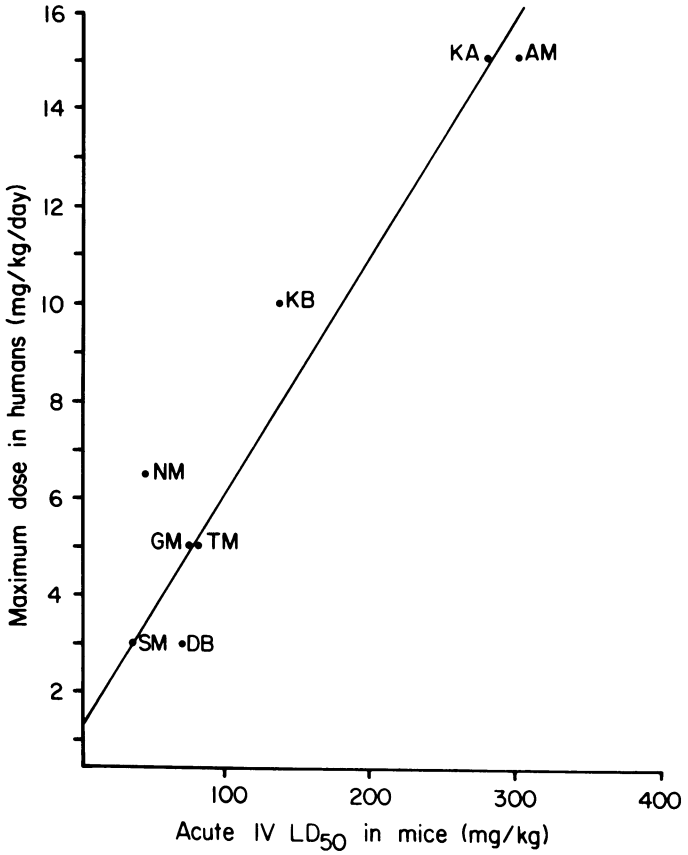

FIG. 1. Relationship between the acute IV LD_{50} for mice and the recommended maximum daily dose for humans. Points: SM, sisomicin; DB, dibekacin; GM, gentamicin; TM, tobramycin; NM, netilmicin; KB, kanamycin B; KA, kanamycin A; and AM, amikacin.

COMPARATIVE DATA ON AGs UNDER DEVELOPMENT

The properties of a number of AG candidates that have undergone extensive preclinical study or which have actually been investigated in humans are reviewed below. These compounds have been categorized by general structural class, i.e., the properties of gentamicin C-related derivatives or analogs have been compared with those of the parent compound to determine whether modification has in fact produced superior agents. The list of AGs considered, while reasonably comprehensive, is certainly not complete.

The biological properties of the various AGs under consideration are shown in Table 1. Initially, data on gentamicin C and the three structurally related compounds that follow are reviewed. The first published report on gentamicin C (Schering-Plough) appeared in 1963. The compound's MIC_{50} of 0.5 μg/ml for wild-type *P. aerguinosa* was arbitrarily assigned a potency value of 1.0. Examination of enzyme susceptibility test results indicates that the activity of gentamicin C is affected detrimentally by 7 of the 10 enzymes under consideration. Finally, the acute IV LD_{50} in mice of this widely marketed antibiotic was 75 mg/kg.

Sagamicin or gentamicin C_{2b}, marketed by Kyowa Hakko, is unlikely to be developed on a wider scale because of the general similarity of its properties to those of gentamicin C.

Win 42122-2 or 2-hydroxygentamicin C (Sterling-Winthrop) has antipseudomonal activity only one-fourth that of gentamicin C. Its level of acute toxicity, based on its 150-mg/kg LD_{50}, is about half that of gentamicin C, clearly suggesting that it will not be tolerated at a dose fourfold higher than that of the control compound. Unfortunately, data obtained by using classic animal models of toxicity did suggest that Win 42122-2 would be at least four- to eightfold safer than gentamicin C (8, 9). The compound was dropped after clinical study when it became apparent that it had no toxicological advantages over gentamicin C. Thus, the acute IV LD_{50} in mice was clearly more predictive of human tolerance to this compound than were results obtained in tests with rats, guinea pigs, or cats.

The agent hydroxyaminoproprionic acid (HAPA)-gentamicin B must be considered a hybrid compound, because it contains one amino sugar found only in gentamicins and another found only in kanamycins, specifically, kanamycin A. The HAPA group serves a function somewhat similar to that of the 1-*N*-acyl group, hydroxyaminobutyric acid (HABA), which is present in amikacin. Relative to the true gentamicins, HAPA-gentamicin B has weak antipseudomonal activity but is appreciably less toxic when given acutely. Its major attribute, however, is its high level of resistance to enzymatic modification, unquestionably due to the presence of the HAPA side-chain. Although animal tests suggest that the toxic potential of the compound is appreciably lower than that of gentamicin C (26), the clinical development of HAPA-gentamicin B appears to be limited to Japan.

The next AG type comprises sisomicin and two structurally related AGs from Schering-Plough. The antipseudomonal potency of sisomicin is twofold that of gentamicin C. However, it is equally susceptible to enzymatic inactivation and has about twice the toxicity based on LD_{50}s. It is now marketed in many countries, but although approved for human use in the United States, it has never been brought to the marketplace here. This may be due to the fact that, at the very best, it shows no advantage over gentamicin C or tobramycin in terms of therapeutic ratio.

Netilmicin or 1-*N*-ethylsisomicin has antipseudomonal activity that is only one-third or less that of the standard, gentamicin C. However, of 10 inactivating enzymes, only three, AAC (2′), AAC (6′), and AAC (3)-III, are capable of significantly affecting the activity of netilmicin (23). Its toxicity potential as measured by the acute IV LD_{50} is greater than that of gentamicin C and slightly lower than that of its parent, sisomicin. Although classic animal model studies suggested that netilmicin would be markedly less toxic than other members of this class (24, 25, 33), its greater safety is not always clearly demonstrable (4, 11). A possible explanation for the failure of traditional nephrotoxicity studies to accurately predict the potential of the compound to cause human nephrotoxicity has been provided by the data of Hottendorf and his co-workers (12, 13). Using histopathological analysis as the major parameter of comparison, they studied the nephrotoxic potential in rats of gentamicin C, netilmicin, tobramycin, and amikacin at low multiples of the human dose (1 to 7×). In contrast to others who investigated only high multiples of the human dose and reached the conclusion that netilmicin is relatively nontoxic, the Hottendorf group found that under their test conditions, the toxicity potential of netilmicin is at least as great as that of the other AGs tested. This apparent anomaly was explained by the atypical flatness of the dose-response–nephrotoxicity curve observed with netilmicin. The fact that AGs do differ with respect to the slope of their dose-response curves may

TABLE 1. Comparative properties of AG antibiotics

AG type	Antibiotic (yr first reported)	Developer	Relative activity against *P. aeruginosa*[a]	Enzyme susceptibility[b]	Acute IV LD_{50} in mice (mg/kg)	References	Status
Gentamicin C	Gentamicin C (1963)	Schering-Plough	1.0	7	75	23,37,49,51	Marketed worldwide
	Sagamicin (1974)	Kyowa Hakko	0.5	6	93	7,23,32,38	Marketed in Japan
	Win 42122-2 (1977)	Sterling-Winthrop	0.25	6	150	6,8,9,43	Dropped after clinical study
	HAPA-gentamicin B (1978)	Schering-Plough and Toyo Jozo	0.3	2	330	23,26,28,31	Phase 3 in Japan
Sisomicin	Sisomicin (1970)	Schering-Plough	2.0	7	34	23,37,50,51	Marketed worldwide except in the United States
	Netilmicin (1976)	Schering-Plough	0.3	3	40	23,25	Marketed worldwide
	5-Episisomicin (1978)	Schering-Plough	1.7	3	45	23,35,48	Phase 1 (internationally)
Kanamycin A	Kanamycin A (1957)	Bristol-Myers	0.05	8	280	23,37,46	Marketed worldwide
	Amikacin (1972)	Bristol-Myers	0.5	2	300	16,23,36,37	Marketed worldwide
	Butakacin (1977)	Pfizer	0.4	2	240	1,23,42	Dropped after clinical study
	BB-K 311 (1979)	Bristol-Myers	0.25	0	>300	21,23,29	Still in preclinical study
Kanamycin B	Kanamycin B (1958)	Bristol-Myers	0.05	9	132	35,37,45	Marketed worldwide except in the United States
	Tobramycin (1971)	Eli Lilly	2.5	7	79	19,23,37	Marketed worldwide
	Dibekacin (1971)	Meiji Seika	0.5	6	71	23,37,47	Marketed worldwide except in the United States
	Habekacin (1973)	Meiji Seika	0.4	2	80	20,23,37	Phase 3 clinical study in Japan
	Propikacin (1979)	Pfizer	0.25	3	NA[c]	5,40,41	Dropped after clinical study
Fortimicin A (astromicin)	Astromicin (1977)	Abbott and Kyowa Hakko	0.05	2	97	17,23,30	Approved in Japan; dropped in the United States after clinical study
	3-*O*-Demethyl-fortimicin A (1980)	Abbott	0.2	2	90	10,15	Dropped after clinical study

[a] Gentamicin was arbitrarily assigned a value of 1.0.
[b] Number of enzymes among 10 with AG-modifying activity that affect the designated compound.
[c] NA, Not available.

well account for the misleading conclusions drawn for other investigational compounds whose nephrotoxicity potential was estimated solely on the basis of data obtained in high-dose studies. No animal models have been developed in which ototoxicity can be induced at clinically relevant doses of AGs.

5-Episisomicin, which is similar to its parent, sisomicin, in all parameters other than enzyme susceptibility, has had a much slower course of development than netilmicin, suggesting that a commitment to market it on a broad scale has not been made.

The next AG type listed in Table 1 is kanamycin A and derivatives. Amikacin, mentioned above, has antipseudomonal activity which is manyfold greater than that of its parent, kanamycin A, but about twofold lower than that of gentamicin C. Of the 10 AG-modifying enzymes, only 2 affect amikacin, compared with 8 for kanamycin A. Acute toxicity of amikacin, like that of kanamycin A, is approximately one-fourth that of gentamicin C.

Butakacin, which has properties very similar to those of amikacin, was apparently shelved because of its late entry into the field and its lack of commercially exploitable advantages over amikacin.

BB-K 311, prepared at the Bristol-Myers Research Institute in Tokyo, Japan, has only one-fourth the antipseudomonal activity of gentamicin C but is unique in that it is refractory to the action of all known inactivating enzymes. Furthermore, it has a very low level of acute toxicity in mice (personal communication, H. Kawaguchi, Bristol-Myers Research Institute, Tokyo, Japan [1985]). Despite this, it is being moved along the developmental path at a rather modest pace because it shows no benefit over amikacin in terms of antimicrobial potency and, probably of even greater importance, there has not been a clinically significant increase in the incidence of amikacin-resistant isolates despite a decade of use of this AG. This has been true even in hospital situations in which as the first-line AG, it has been used intensively over extended periods (3, 22, 27, 39). In view of this, there does not appear to be an urgent need for the commercialization of BB-K 311 in the near future.

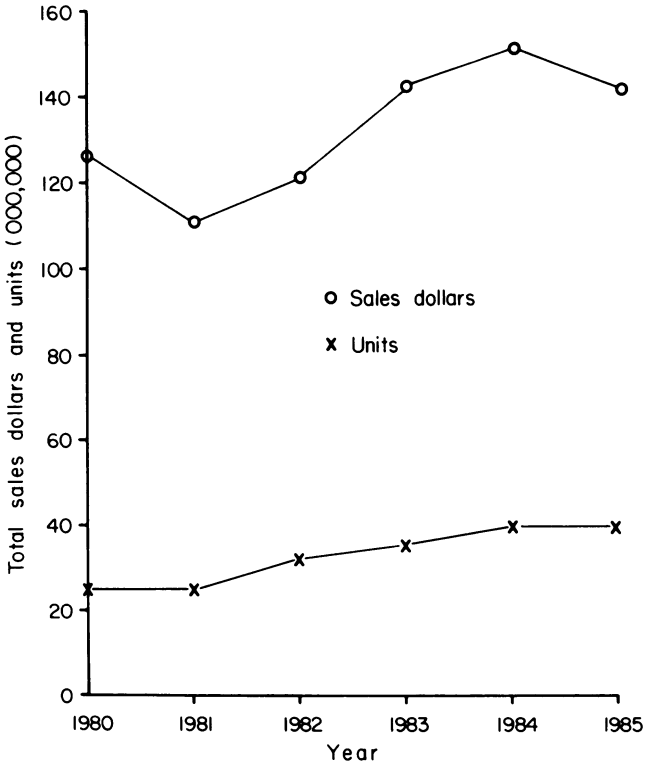

FIG. 2. Annual sales dollars and units of AGs sold in the United States from 1980 to 1985.

The next series of AGs comprises kanamycin B and several of its derivatives and analogs. The parent compound of this series lacks antipseudomonal activity and is modified by many inactivating enzymes. It is twice as toxic as kanamycin A but only half as toxic as gentamicin C.

Tobramycin (3′-deoxykanamycin B) has potent antipseudomonal activity, but unfortunately it is modified by many inactivating enzymes. Absence of the 3′ hydroxyl gives an AG whose toxicity is markedly greater than that of the more completely hydroxylated compound, kanamycin B, and generally comparable to that of gentamicin C, which also lacks a hydroxyl group at the 3′ position.

Dibekacin (3′,4′-dideoxykanamycin B) has properties similar to those of tobramycin, except that its antipseudomonal potency is appreciably lower. In view of the fact that its toxicity potential is at least as great as that of gentamicin C and tobramycin, the human doses of this compound approved for use are predictably similar to those of these two agents. This raises a question as to whether serum levels achieved following such doses of dibekacin are really adequate to treat *P. aeruginosa* infections in seriously ill patients. Its failure to be developed for use in the U.S. marketplace may be a consequence of this concern.

Habekacin or HABA-dibekacin, like HABA-kanamycin A (amikacin), is refractory to most inactivating enzymes. However, because experience has shown that introduction of a substituent into the C-1-*N* position does not usually reduce toxicity potential or improve upon the antipseudomonal potency of a compound, habekacin is unlikely to have a better therapeutic index than dibekacin itself.

The final compound in this series, propikacin, has rather weak antipseudomonal activity but is affected by only three inactivating enzymes. No LD_{50} is available, although it is likely that it would be similar to that of kanamycin B (ca. 130 mg/kg). This compound was taken into the clinic for limited study and then dropped, possibly because its nephrotoxic potential resembled that of currently marketed AGs (2, 5).

The last type of AG examined is made up of two compounds, astromicin (fortimicin A) and its 3-*O*-demethyl derivative. Both possess significant activity against clinical isolates of *Enterobacteriaceae* family species and are quite refractory to inactivating enzymes.

The antipseudomonal activity of astromicin is relatively weak compared with that of gentamicin C. Acute toxicity values for these two antibiotics are very similar, although the ototoxicity and nephrotoxicity potential of fortimicin A, based on results obtained in other animal models, was estimated to be almost an order of magnitude less than that of gentamicin C (17, 44, 52). Although the compound was shelved after brief clinical investigation in the United States, presumably due to the inability to demonstrate a sufficiently low potential for toxicity, it is currently being marketed in Japan.

The 3-*O*-demethyl derivative has antibacterial potency somewhat greater than that of the parent compound. This is particularly evident with respect to antipseudomonal activity, for which it is three- to fourfold better than fortimicin A. As was the case with the latter antibiotic, the 3-*O*-demethyl derivative was found to have a significantly lower potential than gentamicin C (ca. eightfold) to cause toxic effects when studied in traditional animal models (18). Unfortunately, these results did not extrapolate to humans, and development of the compound was discontinued after limited study in the clinic.

PROJECTED ROLE OF AGs

The utilization rate of AGs in the future can best be estimated by considering the usage pattern of this class of antibiotics over the past 5 years. A plot (Fig. 2) shows AG sales dollars for each of the 5 years from 1980 through 1985 (14), as well as the number of units sold in the United States during those years (personal communication, R. Bloem, Bristol Laboratories, Syracuse, N.Y. [1985]). The values for 1985 were estimated on the basis of numbers available for the first three quarters of the year.

Although the amount of sales dollars dropped significantly between 1980 and 1981 due to the introduction of less costly generic forms of gentamicin C, the number of units sold during this period remained constant. There was an increase in both sales dollars and units sold between 1981 and 1984. The 6% dropoff in sales dollars between 1984 and 1985 was strictly a consequence of price erosion, because the number of units sold was the same in both years. However, it is clear that growth has ceased, and volume has, indeed, leveled off. International sales of AGs during these same 2 years show a similar pattern (personal communication, R. Bloem [1985]). This leveling off is almost certainly attributable to the use of alternate agents such as expanded-spectrum cephalosporins. Despite this penetration into the market, it seems unlikely that there will be a rapid or precipitous decrease in the volume of AGs used, because virtually all clinicians still perceive members of this class of antibiotics to be highly potent and efficacious antibacterial agents. Furthermore, the high degree of predictability associated with AG usage with respect to the types of toxicity that can be anticipated provides a certain comfort level to clinicians who are aware of the monitoring tests that must be performed to minimize the occurrence of side effects. This is in contrast to the case with newer agents of other classes, e.g., carbapenems and

quinolones, which do not yet have fully defined side-effect profiles.

CONCLUSIONS

Although it is evident that some derivatives and analogs of gentamicin, sisomicin, the kanamycins, and the fortimicins have markedly improved microbiological properties, none of those described during the past 10 years have shown superiority to amikacin, either with respect to potential to produce toxicity or in terms of therapeutic benefits. Furthermore, because no new major candidates have come to the forefront during the past 5 years, it seems safe to say that the present armamentarium of AGs is all that will be available for use in the future. This is almost a certainty in view of the diminished or terminated AG research activities of companies such as Eli Lilly & Co., Abbott Laboratories, Schering-Plough Corp., Bristol-Myers Co., Sandoz, Inc., and Pfizer, Inc.

Finally, based on the current pattern of usage, it seems likely that AGs will continue, certainly over the next several years, to act as one of the mainstays of therapy for the immunocompromised, seriously ill patient.

ACKNOWLEDGMENTS

I extend my sincerest thanks to those pharmaceutical company colleagues who contributed to this article by providing candid, nonofficial assessments of the current status of many of the developmental compounds discussed herein.

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