Toxicology Letters, 52 (1990) 227–251
Elsevier

TOXLET 02358

Minireview

Aminoglycoside-induced ototoxicity

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(Received 14 August 1989)
(Revision received 27 November 1989)
(Accepted 9 February 1990)

Key words: Aminoglycoside antibiotics; Side effects; Ototoxicity; Sensorineural hearing loss, drug-induced; Epidemiology; Pathology; Pharmacokinetics; Pharmacodynamics

SUMMARY

One of the major side effects of aminoglycoside antibiotics (AG) is ototoxicity. The authors review the literature revealing many controversies on every aspect of this side-effect. Although epidemiological studies have to face the problem of reliable evaluation techniques, the incidence of cochleo- and vestibulotoxic side-effects has been estimated at 7.5% for each. Netilmicin appears to be less ototoxic. No definite risk factors can be proposed, although age, length of therapy, bacteremia, fever, liver and renal dysfunction are probably very important parameters. Most pathological changes at the cochlear level follow a clear spatial sequence, showing unspecific, degenerative lesions, involving every structure of the cochlea. This makes it impossible to draw etiopathological conclusions. Recent pharmacokinetic studies have rejected the 'accumulation theory' of AGs in perilymph, while also in endolymph no accumulation can be found. Only a few data are available on inner ear tissue levels. Among the different pharmacodynamic hypotheses on the action of AGs, binding of the drug to acidic glycosaminoglycans in the stria vascularis, and interference by the drug with phosphoinositide metabolism in the hair cells seem to be of major importance.

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frequency to a unilateral hearing loss of 20 dB at two frequencies. None of these criteria is very specific, which is demonstrated by Smith et al. [25] who reported a 13% incidence of control patients who met the criterion of a 15 dB loss at one frequency or by Davey and Harpur [26] who reported 4 out of 27 patients showing transient threshold changes of 20–35 dB at two or more frequencies without any ototoxic agent being administered. An additional problem is the fact that AGs are mostly, if not exclusively, administered to people who are suffering from severe infections, debilitating them to a great extent and rendering them quite unsuitable for study at all. This may explain in part the intra- and intersubject variability that one encounters in the different studies. For a good evaluation of cochlear toxicity, it is of great importance to perform the first audiometric test before or within the first 48 h after AG therapy has been started. As much as 25% [27] and even up to 66% [28] of hospitalized patients may show pre-existing auditory dysfunction. A drawback of almost all reports is that hearing thresholds are measured only up to 8 kHz, while sufficient evidence exists that AG-induced hearing losses first occur at higher frequencies [29].

Vestibular toxicity might even be more difficult to measure. Many tests have been used to evaluate vestibular toxicity, all of which have been interpreted in different ways (sometimes very vaguely defined) by different authors. It has been suggested that the only good vestibular examination is rotational stimulation with electronystagmographic recording [30]. Doubt can be cast on the feasibility of this type of investigation because AGs are most often given to patients who are in too bad a clinical condition for such an awkward test. The question is whether if a rotational test is impossible, caloric stimulation might be sufficiently reliable to evaluate vestibulotoxicity. Many authors appear to answer this question positively [31–39].

Ototoxicity incidence

Many investigators have examined the incidence of cochleo- and vestibulotoxic side-effects of several AGs. The global incidence of symptomatic ototoxicity has been estimated at 2%, and of asymptomatic ototoxicity at 10% [40]. Clinical studies published between 1975 and 1982 were reviewed by Kahlmeter and Dahlager [41]. Table II lists studies which have been published during the last decade. Figures in bold indicate that the data were obtained from prospective trials. It is impossible to introduce a single common 'ototoxicity criterion' for all these studies. If we accept the criteria as used by the different authors, the overall incidence of cochleo- and vestibulotoxicity can be recalculated, the result being shown in Table III.

On the assumption that gentamicin, tobramycin, amikacin and netilmicin are prescribed to the same extent, one can postulate a 7.5% AG-induced cochleotoxicity with a similar percentage for vestibulotoxicity. Despite a very clear and constant tendency of netilmicin to less cochleo- and vestibulotoxicity than other AGs, and in contrast to animal studies, this difference has never been statistically significant in humans, except in one study where netilmicin was less cochleotoxic than tobramycin ($P=0.037$) [55]. It has to be mentioned that the design of the statistically analyzed

(text continued p. 234)

Bonain's solution
Bromocriptine [13]
Bumetanide
Butikacin

Caffeine
Camphor [10]
Capreomycin
Carbamazepin
Carbon monoxide
Chloramphenicol
Chlorhexidine [14,10]
Chlormethine
Chloroform [10]
Chloroquine
Chlorpheniramine [9]
Chlorphentermine
Chlortetracycline
Cisplatin
Clonazepam
Colistin
Co-trimoxazole
Cyclazine [9]
Cyclophosphamide [15]
Cycloserine [16]

Danazolol [17]

Fenoprofen [9]
Fluorocitrate
Formaldehyde-gelatin sponge
Formalin
Framycetin
Furosemide

Gallium nitrate
Gelfoam [10]
Gemfibrozil [9]
Gentamicin
Gentamicin G-1
Gold salts
Gramicidin
Griseofulvin

Hexadimethrine
Hydroxychloroquine [9,14]

Ibuprofen
Imipramine [9]
Indacrinone [11]
Indomethacin
Insulin
Iodine [10]
Iodochlorhydroxyquinolone

Nalidixic acid
Neomycin
Netilmicin
Nicotine
Nitrogen mustard [11,16,20]
Nitroprusside [9]
Nitrous oxide
Nortriptyline
Novocaine [10]

Oral contraceptive agents
Ouabain
Oxamniquine
Oxyphenbutazone [9]
Oxytetracycline
Ozolinone [11]

Paromomycin
Penicillamine [9]
Perhexiline
Phenobarbital
Phenothiazines
Phenylbutazone
Phenytoin
Piretanide [11,15]
Piroxicam [9,21]
Poliomyelitis vaccine (oral)

Streptomycin
Sulfasalazine [9]
Sulindac [9]

Tetanus toxoid
Tetracaine [9]
Tetracycline hydrochloride
Thalidomide [20]
Thiethylperazine [9]
Thiosulfil [9]
Timolol [9]
Tobramycin
Tolmetin
Tranexamic acid
Tranylcypromine [9]
Tricyclic antidepressants
Trimeprazine [9]
Trimipramine [9]

Vancomycin
Vinblastine [11,18]
Vincristine [11,18]
Viomycin
Vitamin A

* Modified from Lien et al. [8] by courtesy of the Editors of *Journal of Clinical and Hospital Pharmacy*.

Amikacin	1548	5.11	0.65		
	328	**3.35**		Subpopulation	[57]
Amikacin	**29**	**3**			[45]
Amikacin	**14**	**28.5**	**19**		[35]
Amikacin	**29**	**24.1**	0		[58]
Amikacin		1.5-20	0	Review of literatue	[48]
Amikacin	55	18.2		Granulocytopenic patients	[59]
Amikacin		5.7		Review of literature	[16]
Amikacin	35	0.9		Neonates, BERA	[60]
Amikacin	**50**	**0**		Neonates, BERA	[61]
Amikacin	**52**	**7.7**			[37]
Amikacin	**34**		**11.7**		[37]
Amikacin	**54**	**5.8**	**10.8**		[38]
Amikacin		13.9		Review of literature	[11]
Amikacin	14	0	0	Only subjective symptoms recorded	[53]
Sisomicin		1.4	2.9	Review of literature	[48]
Netilmicin	**23**	**13**			[62]
Netilmicin	**29**	**3**			[45]
Netilmicin	**19**	**15.8**	**0**		[35]
Netilmicin	**34**	**8.8**	2.9		[58]
Netilmicin	**76**	**0**	**1.32**	Light, transient vestibular dysfunction	[32]
Netilmicin	**30**	**0**	**(72)**		[34]
Netilmicin	**168**	**0.6**			[47]
Netilmicin	**1200**	**2.5**		Review of literature	[63]
Netilmicin	**84**	**3**			[55]
Netilmicin	**67**	**7.4**			[56]
Netilmicin	**49**	**0**		Neonates, BERA	[61]
Netilmicin	**37**		**0**	Neonates, 3 with high serum levels	[39]
Netilmicin	**50**	**2**	**0**		[38]
Netilmicin		2.4		Review of literature	[11]

Figures in bold represent prospective studies. Figures in brackets represent approximate values. n = number of patients; Co.T = percentage of patients showing cochleotoxicity; Ve.T = percentage of patients showing vestibulotoxicity; HFA = high-frequency audiometry; BERA = brainstem electrical response audiometry.

TABLE IV

RISK FACTORS FOR AMINOGLYCOSIDE OTOTOXICITY

	[62]	[31]	[48]	[59]	[76]	[37]	[77]	[78]	[10]	[51]	[79]
Age		−		−	−		+		(−)	+	+
Sex				+	−		−		−		
Weight				−							
Length of therapy			+	+	+		−				+
Total dose		+	+	−	−		+	+	+		+
Mean daily dose			+	+	−			+		+	
Dose per kg		−	−	−							
Initial audit dysfunction	−		−	−		−			(−)		
Initial creatinine		−			−		−		+		+
Initial creatinine clearance					−				+		+
Renal dysfunction		+			+	⊕	−			+	
Concurrent nephrotoxicity				−		−					
Liver dysfunction					+		−				
Fever		+			+		−				+
Hematocrit					−						+
Bacteremia					+		−				
Urinary tract infection				−							
Pneumonia					−						
Shock					−		−				
Diabetes					−		−				
Otitis media								+			+
Type of aminoglycoside					−		+				+
Mean serum peak	−	−			−		−	+	−	(+)	
Mean serum trough	−	−		−	−	⊞	+	+	−		
Initial serum peak					−						+
Initial serum trough				−						+	
Initial bicarbonate					−						
Previous aminoglycoside		−						+	+	+	+
Furosemide		−	−		−		−	+		+	+
Clindamycin		−			−						
Cephalosporin		−			−		−			+	
Noise		−						+	+		+
Familial predisposition								+	+		
Semistarvation											+

Numbers at top are references. Circle = only cochleotoxicity; square = only vestibulotoxicity. Figures are placed between brackets if the original papers mention them as 'possible' risk or non-risk factors.

epithelium appear to be secondary to the hair cell degeneration. It is not clear whether strial changes occur as primary or as secondary events.

Sensory hair cells

An excellent review of inner and outer hair cell structure has been given by Lim [80]. Structural changes at the hair cell level are among the most widely described findings in AG ototoxicity. Most papers report hair cell loss as investigated by means of phase-contrast or interference-contrast microscopy [65,74,81–86]. Hair cell damage occurs following distinct sequences [85]. The inner row of the outer hair cells of the basal turn are the most sensitive to ototoxic damage. A progression is seen from basis to apex and from OHC I (inner row of outer hair cells) towards OHC III (outer row of outer hair cells) and subsequently to the inner hair cells [72,83,87]. The starting point of outer hair cell damage in guinea pigs seems to be very distinct. This 'degeneration point' is situated at a distance of about 6–8 mm from the round window. Degeneration starts at this point and progresses rapidly to the round window and at a lower speed to the apex [86]. Federspil described the sequence of ototoxic inner ear damage as follows: (1) hair cells, (2) Deiters' cells, (3) pillar cells, (4) Hensen's and Claudius's cells [85]. Simultaneous damage to strial tissue is mentioned, which is confirmed by Gratacap et al. [87]. The spiral ganglion only shows signs of degeneration at a later stage. Early changes can be seen in the auditory hairs [80,88]. Lim remarked the similarity of these findings to acoustic inner ear damage and believes impaired protein synthesis to be a possible common basis for these pathologies. Reports which are based only on qualitative studies mention morphological changes in the lysosomes, which increase in number and size [87], especially in the infracuticular region of the cell [80]. Similar high concentrations of vesicles are described at the base of the cell after intoxication. It is not very clear whether mitochondria are affected. Gratacap and colleagues could not detect any morphological lesions in the mitochondria [87], whereas Lim described mitochondrial swelling [80].

Reissner's membrane

Vacuolization of the epithelial cells at the endolymphatic surface is described [86, 89]. A remarkable appearance of melanin granules in Reissner's membrane is reported after kanamycin administration in guinea pigs [87].

Stria vascularis

The stria vascularis is known to be responsible for the generation of the positive potential of the scala media. It plays an important role in the transport of fluid and electrolytes (resorption and active secretion of endolymph) and contains many oxidative enzymes necessary in glucose metabolism. Lesions of the stria, therefore, may very well produce major changes in endolymph composition, leading to secondary changes in hair cells. The normal structure of the stria vascularis has been reviewed in detail by Schuknecht et al. [90], revealing some remarkable similarities with the

PHARMACOKINETICS

Due to the highly polar cationic state of AGs, their gastrointestinal absorption is very poor. In contrast, intramuscular and subcutaneous injection results in rapid absorption (peak concentrations in plasma after 15–90 min). Distribution is limited to the extracellular fluid. Concentrations in secretions and tissues are low, except for the renal cortex, the endolymph and perilymph. Binding to plasma albumin is negligible. AGs are excreted almost entirely by glomerular filtration, the plasma half-life in humans averaging 2–3 h.

Perilymph

Soon after the discovery of AGs, it became clear that the action of the ototoxicity had to be situated at the periphery, i.e. in the labyrinth [4]. Early attempts were made to establish pharmacokinetic studies on AGs in inner ear fluids [5–7]. The results of these and other studies can be compressed into three major topics.

The first topic is the postulation of a so-called 'toxic threshold' of the inner ear for AGs [102,103]. Serum levels of AGs would have to exceed a critical level before they could enter the perilymph. This hypothesis could afterwards be rejected by the pharmacokinetic studies of Federspil et al. [104] and Tran Ba Huy et al. [105], which showed a linear relationship between dose and perilymph concentration.

The second topic is the accumulation of AGs in perilymph and the postulation that this phenomenon might explain the specific nature of ototoxicity. It was observed that after a single administration of the drug, the perilymph concentration equalled the serum level after several hours and exceeded it manifold after 20 h (Fig. 2a) [84,85,104,106]. Perilymph half-life was found to be 10–12 h, compared to a serum half-life of less than 1 h. Repeated administration even enhanced this retention of the drug in the perilymph [104,107], although this phenomenon was not found by Harpur [108], and one might argue that it is merely the result of drug accumulation in the serum [106]. In striking contrast to these many reports, Tran Ba Huy and colleagues, using sensitive radioimmunoassay methods, described a perilymph peak level which was much lower than those described before, and did not find any accumulation of gentamicin (Fig. 2b) [105]. They reported a perilymph half-life of 3 h after a single injection, while this half-life increased significantly after continuous infusion [109]. It is not clear how to explain this difference between the half-life of 3 h and that of 10 h, although Tran Ba Huy and colleagues suggest differences such as choice of species, preparation of animals, and sampling techniques to be possible explanations [105]. In contrast to Chung et al. [110], neither Ohtani et al. [111] nor Dulon et al. [112] found any difference in perilymph kinetics after comparable doses of netilmicin, amikacin and gentamicin, providing strong evidence that other mechanisms must be responsible for the differences in ototoxicity between different AGs.

The third topic in the pharmacokinetic studies on perilymph concerns the dose–response characteristics of the drug. After a single intramuscular injection, gentami-

In conclusion to these many and often quite confusing data, the 'accumulation theory' might appear unable to explain AG-induced ototoxicity. Besides a puzzling controversy about the existence of any accumulation at all, the actually available data are unable to explain the vestibular or cochlear preference of the toxicity of every single AG. Nor can they explain the differences in toxicity between different AGs, since no difference in pharmacokinetics can be demonstrated.

Endolymph

Very few studies have dealt with endolymph levels of AGs. Federspil and colleagues found no major difference between endolymph and perilymph concentration (endolymph concentration being 80–90% of perilymph concentration after 2 and 5 h, respectively) [104]. Tran Ba Huy and colleagues, on the other hand, showed that the endolymphatic compartment behaves as a deeper compartment than the perilymphatic one, with endolymph to perilymph ratios varying between 0.23 and 0.80 [105,114]. The AGs are taken up very slowly and do not show any substantial accumulation in endolymph. On the other hand, endolymph levels do not show any decay in a 15-day period following a 2-day constant subcutaneous infusion [109]. The levels are similar for different doses, implying either that the surrounding tissues act as a 'buffer' to take up most of the drug or that endolymph uptake is a saturable process.

Inner ear tissue levels

Most of the information on inner ear tissue levels of AGs was obtained by Tran Ba Huy et al [115], using experimental animal models. After a single intramuscular administration of 10 mg/kg body wt., no tissue levels could be detected. If the dose was raised to 100 mg/kg, gentamicin could be detected in the inner ear tissues. When peak concentrations were measured after 3 h, the tissue half-life was some 10–13 h. After continous infusion, tissue levels reached plateau values in 3 h time. The level of these plateaux increased in a linear way with the dose administered up to a certain maximum level, at which the tissue uptake appeared to be saturated. The tissue half-life after 3 h of continuous infusion was 7.3 days. The finding of a tissue $t_{\frac{1}{2}}$ of 3 h after a single shot injection, compared to a $t_{\frac{1}{2}}$ of 7.3 days after a 3-h infusion, was very suggestive of a process having occurred in this 3-h interval that was responsible for a decreased clearance of the drug out of the tissue. This process might be internalization and storage of the drug in the cells of the inner ear tissues. Biochemical assays on inner ear explant culture [116] and tissue homogenates [76] showed that the binding of AGs to inner ear tissues is a high-affinity, rapidly saturable phenomenon. No correlation could be found between tissue levels of different AGs and their ototoxic potential [112].

PHARMACODYNAMICS

Since pharmacokinetics appeared not to be able to explain every aspect of AG-

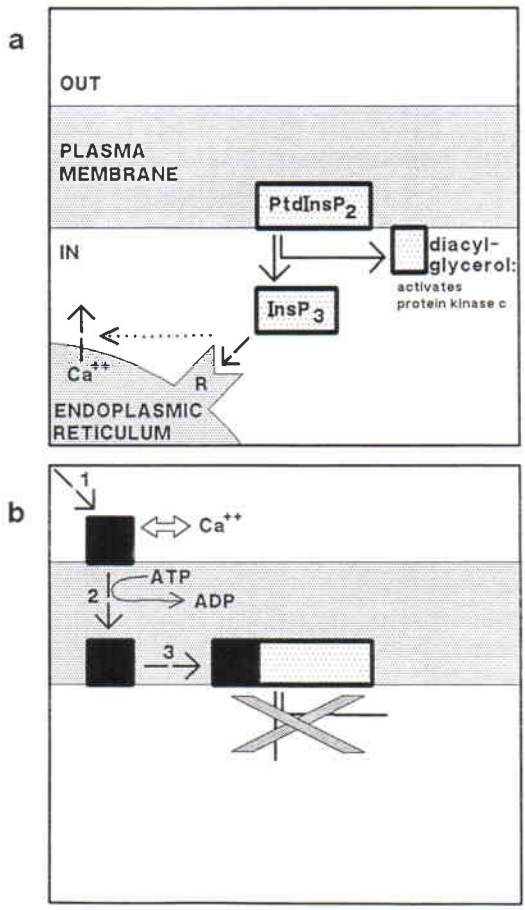

Fig. 3. Graphic representation of the hypothetical role of aminoglycosides in phosphoinositide metabolism. (a) Simplified representation of normal phosphoinositide metabolism. PtdInsP2, a phospholipid which is located in the inner leaflet of the plasma membrane, is cleaved into diacylglycerol and InsP3, both products playing important roles in cellular functions. One of the functions which might be of particular interest in outer hair cells is calcium release out of the endoplasmic reticulum. (b) Interference by aminoglycosides with the former metabolism has been suggested to follow 3 successive stages: (1) binding of the aminoglycoside (black box) on the plasma membrane, in competition with calcium; (2) active transport of the aminoglycoside through the plasma membrane, possibly via polyamine transport systems; (3) binding of the aminoglycoside to PtdInsP2, thus eliminating metabolization of this component. PtdInsP-2 = phosphatidylinositol 4,5-diphosphate; InsP3 = inositol triphosphate; R = InsP3-receptor on the endoplasmic reticulum.

nase C play a crucial role in signal transduction for a variety of biologically active substances which activate cellular functions and proliferation [125,126]. A possible mechanism for which InsP3 might be a second messenger has been speculated to be the calcium-dependent mobile response of outer hair cells [127]. This remarkable con-

Localization

Only a few studies have investigated the localization of AG in inner ear tissues. One of the reasons could be the extremely difficult handling and processing of the specimens for this kind of study. As Wedeen and colleagues pointed out, AGs are very hydrophilic molecules, which are easily displaced by processing in aqueous solutions, as long as they are not firmly bound to structures within the specimen [137]. Most of the studies, however, are based on aqueous processing procedures, while only three studies could be retrieved in which the specimens were snap-frozen, and consecutively sectioned with a cryostat [138], or freeze-dried and embedded [139,140]. Von Ilberg and colleagues compared the freeze-drying technique with aqueous fixation and embedding and found marked differences [140].

After single administration, AGs appear at first in the stria vascularis and in the ligamentum spirale [139]. Between 1 and 3 h after administration, they also appear in the perilymph and in the organ of Corti [139], in which primarily the Deiters cells are strongly stained, while afterwards outer hair cell staining exceeds that of Deiters' cells [141]. Concentrations start to decrease some 6 h after administration. After perilymphatic perfusion, maximum staining is seen over the inner and outer hair cells, basilar membrane and nerve tissue of the spiral lamina [89,140]. Daily administration of high-dose AGs yields staining of Reissner's membrane and basilar membrane during the first 2 days. On the 3rd day of administration, selective staining of the apex of the outer hair cells of the basal turn is described [142].

ACKNOWLEDGEMENTS

The authors are grateful to Mr. Dirk De Weerdt for drawing the figures. This work was supported by a research grant from the University of Antwerp.

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