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Drug-Related Nephrotoxic and Ototoxic Reactions

A Link through a Predictive Mechanistic Commonality

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Abstract

Background: Drug-induced ototoxicity is a subject of interest because many diseases are treated with drugs that have potential toxic effects on the ear. There is evidence that both inner ear and kidney tissue are immunologically, biochemically and functionally related. It has been suggested that drugs that influence the transport of sodium and/or potassium change ionic homeostasis in the inner ear and, hence, induce functional disturbances such as hearing loss, tinnitus and vertigo.

Objectives: To assess whether renal suspected adverse drug reactions (sADRs) have predictive value for ear and labyrinth adverse drug reactions (ADRs) and whether drug classes involved have influence ion transport systems.

Study design: Data were obtained from the Netherlands Pharmacovigilance Centre Lareb. The study base comprised all reports of sADRs up until 1 January 2007. Cases were all sADRs for relevant renal disorders and all sADRs for relevant ear disorders. All other reported sADRs were selected as 'non-cases'. The relationship between drug classes and renal, ear and labyrinth sADRs was evaluated by calculating reporting odds ratios (RORs). An ROR ≥1.50 was regarded as a cut-off value for an association. Drug classes were classified into four groups: (A) ROR kidney <1.50 and ROR ear <1.50 or no reports on ear sADRs (reference group); (B) ROR kidney <1.50 and ROR ear ≥1.50; (C) ROR kidney ≥1.50 and ROR ear <1.50 or no reports on ear sADRs; and (D) ROR kidney ≥1.50 and ROR ear ≥1.50. For each group, we calculated odds ratios (ORs) for the association between the group classification and the effect on ion channels/ion transport systems in kidney and ear tissues.

Results: Of 193 drug classes with relevant ADRs for renal disorders, 120 drug classes also had reports on ototoxic reactions. Fourteen out of 120 drug classes had an ROR ≥1.50 for the association between the drug class and both renal and ear sADRs. Among these drug classes were several with a well known ability to induce renal (adverse) effects and ear and labyrinth disorders, such as loop diuretics, aminoglycosides and quinine. We found that one mechanistic common-

ality of the drug classes mentioned in the reports was the ability to affect ion transport systems. The percentage of drugs having this property differed between the four groups. The ORs for groups D and B were significantly higher compared with the reference group (OR 12.2, 95% CI 3.0, 30.5 and OR 8.7, 95% CI 2.4, 18.7, respectively), whereas there was no association for group C.

Conclusion: Our data suggest that renal sADRs as such are not a marker for drug-induced ear and labyrinth disorders. However, the ability of drugs to act on ion channels or ion transport systems and, therefore, have an influence on ionic homeostasis in the kidney and ear might be a predictor for the possible occurrence of drug-related ototoxicity.

Background

In daily medical practice, drug-induced ototoxicity is a subject of interest because numerous diseases are treated with drugs that have potential toxic effects on the ear.[1] For several drugs, such as aminoglycosides, quinine, salicylates, loop diuretics and antineoplastic drugs, the association with ototoxic effects has been well documented.[1-3] However, there is little evidence for many other drugs. Usually, ototoxic effects have not been detected by the time a drug reaches the market because pharmacological effects on the ear are not routinely evaluated in pre-clinical tests and clinical trials,[4-6] and such effects may be rare. Furthermore, rates of occurrence of ototoxicity are difficult to determine because of the lack of standardized guidelines for monitoring aural function during treatment with potentially ototoxic agents and the wide differences in individual susceptibility.[7,8] The reported incidences of drug-induced ototoxicity vary widely, ranging, for example, from 10% to 63% for aminoglycosides, from 0% to 16% for macrolides and furosemide and from 3% to 100% for platinum antitumour compounds.[7]

Ototoxicity can be defined as the tendency of certain drugs and other chemical substances to cause functional impairment and cellular degeneration of the tissues of the inner ear. The main sites of such ototoxic effects are the cochlea, vestibulum and stria vascularis.[2] Ototoxicity is clinically characterized by tinnitus, hearing loss and vestibular complaints, and has been associated with both short- and long-term exposure.[9,10] Reported risk factors for drug-induced ototoxicity are the patient's age (the young and the elderly are at a higher risk), previous use of an ototoxic agent, dose, exposure to multiple ototoxic drugs and impaired liver or renal function.[7,8] In particular, the relationship between impaired renal function and hearing loss is notable. Firstly, there are inherited renal diseases that are accompanied by hearing disorders, such as Alport syndrome and Bartter syndrome.[11] Secondly, the incidence of hearing loss is considerably higher among patients with chronic renal failure than in the general population.[12] Lastly, the renal adverse effects of some drugs (e.g. aminoglycosides and loop diuretics) can be accompanied by ototoxicity. It has been shown that both kidney and inner ear tissues are to some extent immunologically, biochemically and functionally related.[13] For example, the stria vascularis and the tubular epithelium in the kidney have similar ion transport processes,[14] and the chloride ion channels of the ClC-K family are expressed exclusively in the kidneys and ears.[13,15,16]

Taking these similarities into consideration, it is clinically relevant to know whether the potential renal adverse effects of drugs, which are routinely monitored for, have predictive value for ear and labyrinth adverse drug effects, which are not routinely monitored for.

Thus, the first aim of this study was to assess whether there is an association between renal adverse effects and ear and labyrinth adverse effects as mentioned in spontaneous reports of adverse drug reactions (ADRs) to the Netherlands Pharmacovigilance Centre Lareb. Subsequently, we investigated whether the drug classes involved had a mech-

anistic commonality, namely the ability to influence ion transport systems in kidney and ear tissues that could explain a possible association.

Methods

Setting

The Netherlands Pharmacovigilance Centre Lareb maintains the spontaneous ADR reporting system in the Netherlands on behalf of the Dutch Medicines Evaluation Board. Each year, Lareb receives approximately 6000 reports of suspected ADRs (sADRs), provided by health care professionals, patients and the marketing authorization holders of drugs that are approved for marketing in the Netherlands. Reports contain information about the patient (i.e. age, sex), one or more sADRs, medication used at the time of the event (both suspected and concomitant drugs), source (physician, pharmacists or patient) and the year of reporting. Each report is evaluated by a trained physician and/or pharmacist and filed in a database. ADRs are coded according to the *Medical Dictionary for Regulatory Activities* (MedDRA[1]) terminology; the drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system.[17]

Selection of Case Reports

The study base comprised all reports of sADRS received by Lareb between 1 January 1985 and 31 December 2006. *A priori*, two of the authors (BV and EvP) selected the relevant terms for renal disorders and relevant ear and labyrinth disorders. Subsequently, we selected all sADRs for relevant renal disorders according to the MedDRA terminology among the reported sADRs in the database (see table S1 in the supplementary material ['ArticlePlus'] at http://drugsafety.adisonline.com). All reported sADRs for renal disorders were defined as cases. All other ADRs (i.e. those not classified as relevant renal disorders) were selected as non-cases. Additionally, we selected all sADRs for relevant ear and labyrinth disorders (see table S2 in the online supplementary material) and defined them as cases. All other sADRs (i.e. those not classified as relevant ear and labyrinth disorders) were selected as non-cases.

Data Analysis

The relationships between drug classes and reports with renal sADRs and ear and labyrinth sADRs, respectively, were evaluated by calculating ADR reporting odds ratios (RORs) with 95% confidence intervals (CI). This method, using the concept of 'reaction proportion signalling', assesses whether drugs or drug classes have a disproportionate share in a certain ADR relative to all other reported ADRs.[17] An ROR significantly higher than 1 indicates a disproportionate share of a certain drug or drug class in the reporting of a certain event (i.e. renal or ear disorders) and is, therefore, considered a proxy for an increased risk of the ADR of interest.[18]

An arbitrary point estimate of 1.50 was regarded as an indication for a clinically relevant association between a drug class and renal and ear disorders. As the power of this study was expected to be low because of the small number of reports on nephrotoxic and ototoxic reactions, we decided not use the lower limit of the 95% CI as the cut-off value. Based on the RORs for renal and ear and labyrinth disorders (ROR kidney and ROR ear, respectively), drug classes were classified into four categories: group A – ROR kidney <1.50 and ROR ear <1.50 or no reports on ear sADRs (reference group); group B – ROR kidney <1.50 and ROR ear ≥1.50; group C – ROR kidney ≥1.50 and ROR ear <1.50 or no reports on ear sADRs; and group D – ROR kidney ≥1.50 and ROR ear ≥1.50.

In the search for mechanistic similarities, we focused on the mechanism of actions of drugs with regards to their ability to affect ion transport processes in kidney and ear tissues. We conducted a survey in the medical literature indexed in MEDLINE/PubMed. We used the following Medical

1 MedDRA is a registered trade mark belonging to the International Federation of Pharmaceutical Manufacturers Associations.

Subject Headings (MeSH): 'ion transport' and 'ion channel' in combination with the names of the drug classes (for drug classes, see tables S3–S6 in the online supplementary material) or the name of an individual drug belonging to the related drug class, each with and without 'kidney' or 'ear' as the search limiter. For each of the four groups, we calculated the percentage of drug classes with effects on ion transport systems. We also calculated odds ratios (ORs) with the 95% CIs for the association between the group classification (i.e. A, B, C and D) and effect on ion channels/ion transport systems.

Results

The selection of all relevant sADRs for renal disorders resulted in 1068 reports, in which 193 drug classes were involved. Renal failure was the most frequently reported renal sADR (n = 431, 36.3%), followed by urinary tract signs and symptoms (n = 203, 17.1%). Relevant sADRs for ear and labyrinth disorders were found in 727 reports, in which 160 drug classes were mentioned. Inner ear signs and symptoms were the most frequent ear and labyrinth sADRs (n = 512, 37.5 %), followed by auditory nerve disorders (n = 365, 26.8%) and hearing losses (n = 203, 14.8%).

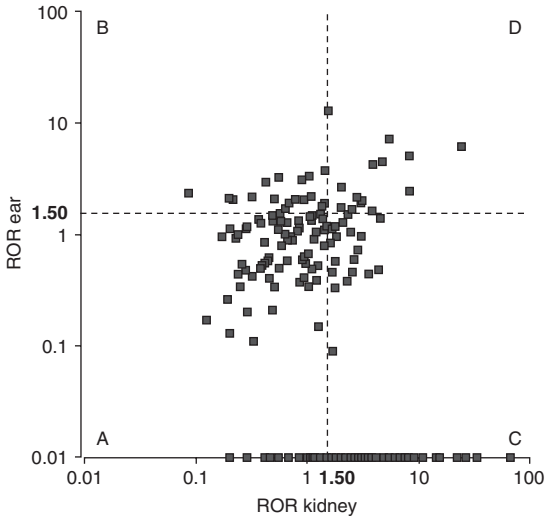

Fig. 1. Reporting odds ratio (ROR) kidney vs ROR ear (n = 193), logarithmic scale. ROR ear of 0.01 indicates no reports of suspected adverse drug reactions (sADRs) involving the ear. Drug classes were classified into four categories: group A – ROR kidney <1.50 and ROR ear <1.50 or no reports on ear sADRs (reference group); group B – ROR kidney <1.50 and ROR ear ≥1.50; group C – ROR kidney ≥1.50 and ROR ear <1.50 or no reports on ear sADRs; and group D – ROR kidney ≥1.50 and ROR ear ≥1.50.

All 193 drug classes were categorized into four groups using an ROR of 1.50 as cut-off value. Of the 193 drug classes with relevant sADRs for renal disorders, 120 drug classes (62.2%) also had reports on drug-related ototoxic reactions. Fourteen out of these 120 drug classes had an ROR ≥1.50 for the association between the drug class and both renal and ear and labyrinth sADRs (figure 1, group D). The drug classes in group D with a disproportionate share in the total number of case reports of both renal and ear sADRs (ROR ≥1.50) are listed in table S6 (supplementary online material). Among these drug classes were several with a well known ability to induce renal (adverse) effects and ear and labyrinth disorders, such as loop diuretics, aminoglycosides and quinine. For seven out of the 14 drug classes with an ROR ≥1.50 for the association between drug class and both renal and ear sADRs, terms that indicate ear and labyrinth disorders, such as tinnitus, hearing loss and vertigo, are listed in the summaries of product characteristics (SPCs). Specifically, these were: high-ceiling diuretics, other peripheral vasodilators, other aminoglycosides, glycopeptide antibacterials, quinine (derivatives), salicylic acid (derivatives) and carbonic anhydrase inhibitors (see table S6, numbers 4, 5, 6, 7, 10, 12 and 13).

In the search for a mechanistic commonality as an explanation for this observed association between spontaneous reports on renal and ear and labyrinth sADRs, we assessed whether the drugs involved had any mechanisms of action in kidney and ear tissues. In group D, several drug classes act on membranes influencing the transport of sodium and/or potassium, chloride and calcium via direct or indirect pathways. These are locally acting corticosteroids, high-ceiling diuretics, other aminoglycosides, quinine (derivatives), salicylic acid (derivatives) and carbonic anhydrase inhibitors (numbers 1, 4, 6, 10, 12 and 13, table S6 in the supplementary online material). Well known ototoxic and nephro-

Table I. Association between group classification (based on reporting odds ratio [ROR] kidney and ROR ear) and the effect on ion transport systems

Group	Group definition	No. of drug classes in group	Drug classes with effect on ion transport systems [n (%)]	OR (95% CI)
A	ROR kidney <1.50; ROR ear <1.50 or no reports on ear sADRs	86	5 (5.8)	1.00 (reference)
B	ROR kidney <1.50; ROR ear ≥1.50	20	7 (35.0)	8.7 (2.4, 18.7)
C	ROR kidney ≥1.50; ROR ear <1.50 or no reports on ear sADRs	73	8 (11.0)	2.0 (0.6, 3.1)
D	ROR kidney ≥1.50; ROR ear ≥1.50	14	6 (42.9)	12.2 (3.0, 30.5)

OR = odds ratio.

toxic drugs, such as loop diuretics, aminoglycosides and salicylic acid (derivatives), are among those drug classes associated with reports of ear and renal sADRs.

The 20 drug classes in group B are listed in table S4 (supplementary online material). Platelet aggregation inhibitors (see table S4, number 1), low-ceiling diuretics (numbers 3 and 4), oxicams (number 12) and quinine alkaloids (number 19) affect ion channels and/or ion transport systems. In contrast to the drug classes in tables S6 and S4, the majority of the number of drug classes with reports on renal and ear sADRs in group C and group A (reference group) [see tables S5 and S3 in the supplementary online material, respectively] have no effect on ion transport systems, at least not in kidney or ear tissue.

In table I, the association between the group in which the drug classes are classified and the effect on ion channels/ion transport systems in kidney and ear tissues is described. The reference group contained those drug classes with reports of renal sADRs with an ROR <1.50 and an ROR ear <1.50 or no reports on ear sADRs. In groups D and B, the number of drug classes with an effect on ion transport systems was statistically significantly larger than in the reference group (OR 12.2, 95% CI 3.0, 30.5 and OR 8.7, 95% CI 2.4, 18.7, respectively), whereas there was no association for group C (OR 2.0, 95% CI 0.6, 3.1).

Discussion

Our main finding was that there was a high percentage of drug classes affecting ion transport systems among drug classes associated with a disproportional share of reported sADRs for both kidney and ear (group D, see table S6 in the online supplementary material). Furthermore, another interesting finding was that also in group B (see table S4), effects on ion systems seem to play an important role. This also applies to the group of drug classes with an ROR ear ≥1.50 and no reports on renal sADRs (OR 4.2, 95% CI 1.3, 7.3; data not shown). This outcome would imply that, regardless of any (reports of) renal sADRs, the ability to act on ion transport systems in the inner ear could be an important factor in drug-induced ototoxicity.

It has been established that many drugs are capable of inducing ototoxicity and nephrotoxicity. The mechanisms by which these adverse effects are produced are not well understood, but kidney and ear tissues may be related on immunological, biochemical and functional levels.[13] In appendix I, the mechanisms of action of the drug classes in groups D and B with regards to ion transport systems are listed. Although there are some indications that other drugs can also act on ion channels,[19,20] the relevance with regards to ion systems in kidney and/or the ear is either unclear or not well established. Other drug classes do have the ability to act on ion transport systems, such as digitalis glycosides (see table S5, number 14, in the online supplementary material) and sulfonylurea derivatives (see table S3, number 7), but there are no indications that they influence ion systems in kidney and/or ear tissues. The importance of ion transport processes in ear tissues is discussed in appendix II.

There are several limitations to this study. Firstly, the selection of the relevant terms for renal disorders

and for relevant ear and labyrinth disorders according to the MedDRA terminology was in part arbitrary. Secondly, the concept of 'reaction proportion signalling' has limitations. A spontaneous reporting system as a means of collecting data on sADRs is known to represent only a fraction of the drug-related adverse events,[21,22] and is dependent on the type of ADR. Selective over- and underreporting of specific ADRs may lead to misinterpretations when comparing drug classes with respect to ADRs. ADRs associated with relatively new drugs, severe ADRs[23] and ADRs that are not listed in the SPC[24] are reported more often than others. Notwithstanding the selective underreporting, drug classes with a known ability to induce ototoxic adverse effects emerged from the Lareb database (see tables S6 and S4). The potential for reporting bias, which is always a concern in this type of study, is, however, low with respect to the research question concerning mechanistic commonalities, since it is not to be expected that reports are made on basis of a suspicion that ion transport systems are involved.

As a consequence of the low numbers of reports for individual drugs, we evaluated the associations on the drug class level. For the majority of drug classes, adverse effects involving the kidney and ear are considered a class effect, but there are some exceptions. For example, minocycline, a tetracycline derivative, appears to produce vestibulotoxicity, whereas other tetracycline antibacterials do not. The same applies for irbesartan and telmisartan, which are able to induce tinnitus, in contrast to other angiotensin II receptor antagonists (information from Dutch SPCs). Because of the low numbers of reports, we could not discriminate between these individual drugs, and we categorized them on the basis of the overall class effect (group A).

In order to study the robustness of our results, we conducted a sensitivity analysis using RORs of 1.00 and 2.00 as cut-off values. Using an ROR of 1.00 resulted in ORs of 6.8 (95% CI 1.7, 13.4) and 2.8 (95% CI 0.6, 5.7) for group D and B, respectively. When using an ROR of 2.00, the ORs were 6.5 (95% CI 1.5, 20.2) and 6.1 (95% CI 1.8, 15.2) for group D and B, respectively. The use of different cut-off values changed the magnitude of the ORs, but did not change our main finding.

Thirdly, all ATC codes were included, regardless of the route of administration of a drug. We did not take into account whether a drug was able to penetrate into the inner ear after administration. This could lead to overestimation of the observed association. Lastly, in this study, we did not adjust the RORs for potential confounding factors, such as patient characteristics, co-morbidity and any co-medication. In the context of studying renal and ear and labyrinth sADRs, age may act as a confounder. Elderly patients are more at risk for drug-induced ototoxicity and impaired renal function, and for exposure to multiple (ototoxic) drugs. In the drug classes with both an ROR kidney and ROR ear ≥1.50, reports of renal and ear and labyrinth sADRs regarding elderly patients may be overrepresented.

In this study, we classified drug classes according to their mechanistic properties in relation with the calculation of RORs. In a study on anti-hERG activity in relation with drug-induced corrected-QT interval prolongation, the same concept was used.[25] However, to our knowledge, there are no other studies of this type, in which the relationship between a combination of two RORs on different organ systems and a corresponding mechanism of action is assessed.

Conclusion

In this study, we focused on the possible association between renal events and ear and labyrinth disorders using a spontaneous reporting system and the mechanistic similarities between drug classes mentioned in those reports. Overall, our data suggest that suspected renal events as such are not a marker for drug-induced ear and labyrinth disorders. However, the ability of drugs to act on ion channels or ion transport systems, and thereby influence ionic homeostasis in the kidney and ear, might be a predictor for the possible occurrence of drug-related ototoxicity. Since in pre-clinical testing, pharmacological effects on ear tissues are not routinely assessed, an important practical implication of our findings could be that drug classes that are able to

act on ion transport systems in kidney and ear tissues might have potential ototoxic properties. However, the number of reports on the drug classes involved in the analysis was low and further research into this field is necessary to clarify the mechanistic commonality in detail.

Appendices

Appendix I: Mechanisms of Action

Loop diuretics (see table S6, number 4, in the supplementary material ['ArticlePlus'] at http://drugsaftey.adisonline.com) are inhibitors of the Na^+-K^+-$2Cl^-$ transport system in the loop of Henle, and *carbonic anhydrase inhibitors* (see table S6, number 13) have a diuretic effect involving the reabsorption of hydrogen carbonate and the excretion of Na^+ and K^+. *In vivo* studies have shown that loop diuretics could induce changes in the electrolyte composition of the endolymph.[26-28] *Thiazides and related diuretics* inhibit the Na^+-Cl^- transport system in the distal tubule (see table S4, number 3, 4 and 6).

Salicylic acid derivatives and NSAIDs (see table S6, number 12, and table S4, numbers 1 and 12) affect the outer hair cells. Their main action is inhibition the prostaglandin synthesis. Prostaglandins are key regulators of ion transport in the kidney and they also regulate the Na^+-K^+ adenosine triphosphate (ATP)ase pump. Because Na^+-K^+-ATPase is present in the cochlea, it is plausible that prostaglandin synthetase inhibitors have an effect on ion transporting epithelia in the inner ear as well.

As with salicylate ototoxicity, quinine ototoxicity appears to be multifactorial in origin.[29,30] *Quinine and derivatives* (see table S6, number 10, and table S4, number 19) induce vasoconstriction and decrease cochlear blood flow. Alterations and loss of outer hair cells seem to play important roles. Antagonism of calcium-dependent K^+ channels may have a potential role in ototoxicity. Blockage of K^+ currents may inhibit the generation of the endocochlear potential.[31]

Calcium antagonists (*benzothiazepine derivatives*, see table S4, number 5) block the L-type voltage-sensitive calcium channels in arterial smooth muscle, causing relaxation and vasodilatation. The L-type calcium channels are present in both cochlear and vestibular receptors.[32]

Glucocorticoids (see table S6, number 1, in the online supplementary material) are involved in the Na^+-K^+-ATPase activity in several tissues, including the stria vascularis in the inner ear.[33] It has been suggested that glucocorticoids regulate Na^+ transport in the inner ear and therefore may be beneficial in the treatment of Ménière's disease.[34,35]

Aminoglycosides (see table S6, number 6, in the online supplementary material) are antibacterials which interfere with the bacterial messenger RNA. They accumulate rapidly in the perilymph and endolymph of the inner ear, where they target the sensory hair cells. They are known to block a variety of ion channels, including large-conductance Ca^{2+}-activated K^+ channels, although blockage is not thought to lead directly to ototoxic effects.[36]

Appendix II: Role of Ion Transport Processes in the Inner Ear

From the literature, it is known that ion transport processes play an important role in both kidney and ear tissues.[13-15] *Changes in ionic homeostasis* in the inner ear may lead to functional disturbances, namely hearing loss, tinnitus and vertigo.[37] The major function of the inner ear is the transformation of mechanical stimuli into electrical signals. This conversion occurs in the sensory hair cells of the cochlea, and the availability of K^+ ions is essential to maintain normal auditory function.[16,38] K^+ is the major cation in endolymph, and the cochlear function depends on the active secretion of K^+ and absorption of sodium (Na^+).[16,39,40] In the cochlea, *Na^+-K^+-ATPase* plays an important role in maintaining ionic homeostasis and physiologic function.

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