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Betahistine

A Retrospective Synopsis of Safety Data

Sabine Jeck-Thole and *Wolfgang Wagner*

Solvay Pharmaceuticals, Hannover, Germany

Contents

Abstract

Betahistine is a structural analogue of histamine that is prescribed for the treatment of vestibular disorders such as Ménière's disease and the symptomatic treatment of vertigo. It is estimated from sales information that >130 million patients have been exposed to the drug since its registration in 1968. In this review we analyse the safety profile of betahistine based on data obtained during >35 years of worldwide postmarketing surveillance.

Until 31 December 2005, 554 adverse drug reaction (ADR) reports with 994 individual signs and symptoms were received by the marketing authorisation holder from worldwide sources and were reviewed and evaluated. Signs and symptoms of cutaneous hypersensitivity reactions during betahistine therapy were the most frequently reported complaints. They consisted of usually mild and self-limiting rash, pruritus and urticaria, and all symptoms were reversible after drug discontinuation. Betahistine was reported to be involved in one anaphylactoid reaction and one case of Stevens-Johnson syndrome. Anaphylactic reactions with fatal outcome were not reported.

The reports that describe gastrointestinal complaints mostly concern nausea and vomiting or unspecific abdominal pain. These were typically non-serious complaints. Hepatobiliary involvement was reported 25 times, including increases in alkaline phosphatase, γ-glutamyltransferase, and alanine and aspartate aminotransferase levels. None of the patients concerned developed severe liver failure or

died. ADRs related to the nervous system predominantly reveal heterogeneous events that are not suggestive of a specific adverse reaction profile for betahistine. A clinical intolerance to betahistine that gave rise to asthma or bronchospasm was only reported in eight ADRs. A total of three cases of neoplasm have been reported. One case concerned a male patient of unknown age who experienced weight loss, insomnia, impatience and irritability soon after the start of betahistine therapy. An undiagnosed phaeochromocytoma was suspected. The remaining two cases were assessed as being unrelated to betahistine by the reporter. Finally, four deaths have been reported during the course of postmarketing surveillance for betahistine. The reporter assessed the causal relationship to betahistine in two as unrelated, in one as unlikely and the other as unassessable.

In summary, clinical and postmarketing studies have revealed a good safety profile of betahistine that was confirmed by the safety surveillance data presented.

Betahistine is a structural analogue of histamine with similar pharmacological properties but without its potential toxicity in terms of anaphylactic reactions. The drug was first registered in Canada in 1968 and, to date, is approved in >80 countries for vestibular disorders such as Ménière's disease and the symptomatic treatment of vertigo. It is estimated that >130 million patients have received betahistine since first launch.

From early observations it was known that intravenous histamine was efficacious for symptom relief in patients with vestibular disorders but also resulted in a high number of adverse effects, some of which were severe.[1] In the tissue, histamine is mainly stored in mast cells and may be released by various drugs or venoms, playing a crucial role in hypersensitivity reactions, gastric acid secretion and increasing capillary permeability. In association with the peripheral actions of histamines, a function as central neurotransmitter was postulated. Subsequently, various receptor subtypes were described, including histamine H_1, H_2, H_3 and recently H_4.[2,3]

Receptor studies have demonstrated that betahistine acts as a neurotransmitter modulator of the complex histaminergic receptor system and has no or negligible affinity for other known receptors.[4] Betahistine is a weak partial H_1 receptor agonist with a distinctly lower affinity than histamine.[5,6] The H_2 receptor affinity is almost negligible as shown in animal studies, for example by its extremely weak effects on gastric secretion[7] and hamster skin permeability.[8]

Betahistine shows a potent antagonistic effect on the H_3 receptor. The H_3 heteroreceptor belongs to a class of presynaptic receptors and is involved in the synthesis and release of histamine and other heterogeneous neurotransmitters including dopamine, GABA, acetylcholine, noradrenaline (norepinephrine) and serotonin.[9] Actions that are mediated by the H_1 receptor are blocked by negative H_3 receptor feedback. The H_3 receptor antagonistic action of betahistine is followed by an increased histamine release.[4] The H_3 receptor antagonistic action of betahistine is regarded as being responsible for improvement of the microcirculation of the inner ear and reduction of the endolymphatic pressure.[10,11] Betahistine inhibits the basal spike generation of the vestibular afferent neurons in the lateral and medial vestibular nuclei,[12] which are crucial for processing the labyrinth and proprioceptor input to control posture.

In animal models of unilateral vestibular dysfunction, it was shown that betahistine enhances histamine synthesis and release within tuberomammillary nuclei and improves vestibular compensation (for review see Lacour and Sterkers[13]). Tighilet et al.[14] studied the neurochemical and molecular mechanisms of betahistine interaction with the histaminergic system in cats. They found that betahistine upregulates the messenger RNA (mRNA) for histidine decarboxylase, very likely by

blocking the presynaptic H_3 receptors, and induces H_3 receptor downregulation. Botta et al.[15] investigated whether betahistine and its metabolites affect the peripheral vestibular receptors in a frog model. They recorded ampullar receptor activity at rest and during mechanical stimulation of the sensory organ. Both betahistine and one metabolite, the aminoethylpyridine, reduced the ampullar receptor resting discharge, which is associated with the pathophysiology of vertigo. The authors hypothesised that the anti-vertigo action of betahistine is first achieved by the parent drug and continued by the metabolite.

Pharmacokinetic studies with ^{14}C labelled betahistine showed that the compound is rapidly and completely absorbed after oral administration, with peak plasma concentration reached after approximately 1 hour. The plasma half-life of total radioactivity is approximately 3.5 hours. The drug is mainly metabolised in the liver and undergoes almost complete first-pass metabolism in healthy volunteers.[16] Due to the rapid metabolism, plasma concentrations of the parent drug are below the detection limit of the assay method. The only metabolite detected in urine and in plasma is 2-pyridyl acetic acid. The histamine metabolism – a ring methylation and an oxidative deamination – is not influenced by betahistine.[17]

Various studies have underlined the efficacy of betahistine in Ménière's disase and vertigo.[18-22]

The recommended daily dose for betahistine is 24–48mg divided in two or three single doses. Betahistine is available as scored or unscored tablets containing 8, 16 or 24mg of betahistine and as a solution for oral administration containing 8 mg/mL of betahistine.

This paper reviews the safety profile of betahistine based on information received through Solvay Pharmaceuticals' global, post-authorisation surveillance system until 31 December 2005. Complementary data that characterise the histamine-like properties of betahistine are provided to verify or falsify potential safety signals.

1. Database Search Methodology

Adverse drug reaction (ADR) reports related to betahistine are collected, processed and analysed from worldwide sources by the marketing authorisation holder (MAH) in line with the International Conference on Harmonisation (ICH) guidelines. The following data are entered in Solvay Pharmaceuticals' global safety database by:

- all serious and non-serious ADR reports spontaneously reported from the market and from regulatory authorities;
- all serious ADR reports available from studies or named-patient use that are attributable to betahistine by investigator or sponsor;
- all serious and non-serious ADR reports from the scientific literature that are identified by means of weekly searches in the literature databases Reactions®, MEDLINE and EMBASE.

In line with international guidelines,[23] reports from clinical studies without a reasonable possibility of a causal relationship between the drug and the adverse event were not considered as ADRs. Subsequently they were excluded in this review. However, all spontaneous reports from the market were regarded as ADRs, irrespective of whether they were considered drug related by the reporter. The ADR reports meeting these criteria and received between market introduction and 31 December 2005 were collated and analysed. The reports have been encoded in Medical Dictionary for Regulatory Activities (MedDRA) version 8.1.

The following events are regarded as being 'serious' ADRs irrespective of the dose administered:

- all fatal events;
- all life-threatening events;
- all events that necessitate inpatient hospitalisation or prolongation of existing hospitalisation;
- all events that result in persistent or significant disability/incapacity;
- all events that are a congenital anomaly or birth defect.

Additionally, ADRs that constituted an important medical event that might jeopardise the patient or might require intervention to prevent any of the outcomes listed in the previous definition were also

considered serious according to the evaluation of medical and scientific experts.

The medical review included coding of ADRs to MedDRA preferred terms by a physician. In case an ADR affected more than one MedDRA body system, the clinically most significant ADR was assigned to the corresponding body system and the other(s) listed with it.

The frequency listing reflects the absolute numbers of reported ADRs. In case of a verified safety signal, the betahistine data were further evaluated and complementary data were provided.

A crude number of exposed patients was calculated. For this purpose the defined daily dosage (DDD) was used according to the guidelines of the WHO Collaborating Centre for Drug Statistics Methodology.[24] The DDD is the assumed average maintenance dose per day used for the main indication of a drug in adults. It is a unit of measurement without necessarily reflecting the recommended or prescribed daily dose. For betahistine, a DDD of 24mg for 40 days was assumed. Based on the DDD and sales volume for betahistine, it is estimated that >130 million patients have been treated with betahistine.

2. Database Search Results

Until 31 December 2005, the Global Drug Safety and Surveillance (GDSS) department at Solvay Pharmaceuticals received a total of 554 individual ADR reports with 994 signs and symptoms during betahistine therapy. The majority (62.1%) were spontaneous reports from the market, followed by reports from health authorities (37.9%). Reports may be obtained from more than one source. In total, 153 reports (27.6%) were assessed as serious either by the reporter or by the GDSS unit.

A summary of individual ADR reports allocated to MedDRA categories is shown in table I. The most frequent ADRs or symptom class of ADRs and events of special interest are presented in table II.

Of all adverse events, 18.1% (n = 180) were reported in the nervous system. Paresthesia was observed in 16 patients and tremor in 18 patients. Headache was reported in 30 patients. Dizziness and vertigo were reported in 51 patients as an adverse event and specified as vertigo in 11 cases.

Skin and subcutaneous tissue disorders made up 17.3% (n = 172) of all events. Different types of rashes were reported in 47 patients, pruritus in 35 patients and urticaria in 29 pateints. Various occurrences of oedema were described in 35 patients.

In total, 12.9% (n = 128) of cases presented with gastrointestinal complaints. Most patients described nausea (n = 30), vomiting (n = 14) and unspecific abdominal pain (n = 17).

Only 3.5% (n = 35) of all events fell into the category of respiratory, thoracic and mediastinal disorders. Asthma, bronchospasm and wheezing were reported in nine patients. In total, 15 patients complained of dyspnoea including one patient with dyspnoea on exertion. Cough was reported in five patients.

A neoplasm was reported or suspected in 0.3% (n = 3) of patients. One case concerned a male patient of unknown age who experienced weight loss, insomnia, impatience and irritability soon after the start of betahistine therapy. An undiagnosed phaeochromocytoma was suspected. The remaining two cases were assessed as being unrelated to betahistine by the reporter.

A total of four deaths during betahistine therapy have been reported. In one case, a 58-year-old male patient suffered a fatal myocardial infarction following a period of angina pectoris. An 85-year-old patient died of cholestatic jaundice and cytolytic hepatitis complicated by renal failure. In a post-authorisation study, an 88-year-old male patient died from myocardial infarction, which developed 8 days after stopping betahistine. A girl whose mother had received betahistine for 10 days during early pregnancy presented with microcephalus, hyperlactataemia and calcification of basal ganglia. She died at the age of 3 years. An inherited mitochondrial defect was suspected.

Since market introduction, eight cases of suspected drug interactions have been reported, including one report from the literature.[25] No drug is mentioned more than once as a possibly interacting compound. These possible drug interactions are dis-

Table I. Number of unique adverse drug reaction (ADR) reports and number of all ADRs received until 31 December 2005 classified by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class

MedDRA System Organ Class	All ADRs[a]		Serious (n)	Unique reports		Serious (n)
	n	%		n	%	
Blood and lymphatic system	23	2.3	18	15	2.7	10
Cardiac	34	3.4	18	17	3.1	8
Congenital, familial and genetic	2	0.2	2	2	0.4	2
Ear and labyrinth	27	2.7	1	19	3.4	0
Endocrine	2	0.2	2	1	0.2	1
Eye	25	2.5	6	15	2.7	6
Gastrointestinal	128	12.9	37	75	13.5	17
General disorders and administration site conditions	105	10.6	36	44	7.9	9
Hepatobiliary	13	1.3	12	7	1.3	6
Immune system	6	0.6	4	5	0.9	3
Infections and infestations	6	0.6	2	1	0.2	0
Injury, poisoning and procedural complications	16	1.6	12	5	0.9	3
Investigations	34	3.4	15	18	3.3	6
Metabolism and nutrition	22	2.2	11	12	2.2	7
Musculoskeletal and connective tissue	21	2.1	4	9	1.6	1
Neoplasms: benign, malignant and unspecified	3	0.3	3	2	0.4	2
Nervous system	180	18.1	58	93	16.8	21
Pregnancy, puerperium and perinatal conditions	3	0.3	3	3	0.5	3
Psychiatric	73	7.3	23	39	7.0	11
Renal and urinary	13	1.3	8	6	1.1	2
Reproductive system and breast	14	1.4	1	13	2.4	1
Respiratory, thoracic and mediastinal	35	3.5	15	22	4.0	7
Skin and subcutaneous tissue	172	17.3	39	114	20.6	20
Surgical and medical procedures	1	0.1	1	0	0	0
Vascular	36	3.6	14	17	3.1	7
Total	**994**	**100.0**	**345**	**554**	**100.0**	**153**

a Individual reports may contain more than one sign or symptom.

cussed in association with betahistine and ethanol, ascorbic acid, potassium bicarbonate/potassium chloride, omeprazole, rofecoxib, terfenadine, cetirizine and celecoxib.

Twelve cases of betahistine overdoses have been reported; three patients presented with multiple drug ingestions. Since market introduction there have been no reports of intentional misuse of betahistine.

The global safety database contains information on six women who received betahistine therapy while pregnant or breast feeding. One patient reported a spontaneous miscarriage and two reported induced abortions. Another case of miscarriage in a study patient was assessed as unrelated to the study drug. Congenital abnormalities were related to three further cases (see section 3.10 for detail). There were only anecdotal reports of betahistine being used in children or adolescents (≤17 years), one in a case of an intentional overdose.

Nineteen ADRs occurred in patients who had been treated with betahistine for >1 year.

3. Discussion

During >35 years of use, safety of betahistine was investigated by data obtained in controlled settings in the case of studies, and in a non-controlled population under everyday conditions.

In general, pre-authorisation trials only identify adverse reactions which are considered common. They occur in ≥1% of patients who are treated with the drug of interest.[26] However, uncommon events

Table II. Frequent adverse drug reactions (ADRs) and drug reactions of special interest

ADR	Total no. reported (% of all reported terms)	ADR	Total no. reported (% of all reported terms)
Dizziness	51 (5.1)	**Urticaria**	29 (2.9)
dizziness	38	urticaria	27
vertigo	11	urticaria pigmentosa	1
balance disorder	2	urticaria generalised	1
Rashes	47 (4.7)	**Hepatobilary involvement**	25 (2.5)
rash	28	hepatobiliary disorder[a]	13
rash maculo-papular	8	hepatic enzyme increased[a]	12
rash erythematous	5	**Tremor**	18 (1.8)
rash papular	3	**Abdominal pain**	17 (1.7)
rash pruritic	1	abdominal pain upper	13
rash generalised	1	abdominal pain	2
rash macular	1	gastrointestinal pain	2
Nausea/vomiting	44 (4.4)	**Dyspnoea**	15 (1.5)
Pruritus	35 (3.5)	dyspnoea	14
pruritus	30	dyspnoea exertional	1
pruritus generalised	3	**Dysaesthesia**	16 (1.6)
eye pruritus	1	paraesthesia	13
pruritus allergic	1	burning sensation	2
Oedema	35 (3.5)	hypoaesthesia	1
face oedema	11	**Overdose**[a]	12 (1.2)
oedema	6	overdose	6
oedema peripheral	7	accidental overdose	4
angioneurotic oedema	4	intentional overdose	2
swelling face	2	**Gastrointestinal bleeding**	8 (0.8)
swollen tongue	2	gastrointestinal haemorrhage	3
swelling	1	rectal haemorrhage	2
oedema mouth	1	gastric ulcer haemorrhage	2
localised oedema	1	haematemesis	1
Headache	30 (3.0)		
headache	28		
tension headache	1		
migraine without aura	1		

a By preferred terms and cluster of preferred terms.

will not emerge in pre-authorisation study settings with just several thousand patients being observed.

Spontaneous case reporting and post-authorisation surveillance involves monitoring, identification, evaluation and response to safety hazards and are able to detect rare and unusual effects presenting in <0.1% of patients. They are a useful tool for generating a large amount of information, which is evaluated and transferred into recommendations for everyday routine use. Post-authorisation studies and surveillance have various limitations. A suspicion is expressed and is not always linked with a precise assessment of causality between the adverse event and the drug. The incoherence of reporting and the inaccuracy and inconsistency of data lead to restrictions and may interfere with an adequate ADR evaluation.[27] The spontaneous reporting system has also been criticised for under-reporting, so that the frequency of a particular event may not be accurately presented.[28] Less serious or infrequent events are regarded as not worth reporting. On the other hand, public interest or media presence may precipitate

reports. A clear report and a systematic ascertainment of data should be the gold standard as advised in the ICH guidelines.[29] The experts who review the data should be independent to minimise bias, and modern computer systems could encourage this with the application of data mining techniques. Thus, the safety profile of a recently launched drug will become more comprehensive over time as adverse reactions are reported spontaneously in a routine clinical context supported by post-authorisation surveillance.[30] The efficacy of the post-approval monitoring procedure may enhance confidence in a drug.

3.1 Deaths

Fatal events have been reported infrequently during betahistine therapy. In one case, a 58-year-old male patient had a fatal myocardial infarction following a period of angina pectoris. Causality between betahistine treatment and the event was reported as not assessable.

An 85-year-old patient presented with cholestatic jaundice and cytolytic hepatitis while he was receiving enalapril, cotrimoxazole (trimethoprim/sulfamethoxazole) and betahistine. He finally developed renal failure and died. All three drugs were suspected in view of causality. A causative role of betahistine involvement was regarded as being unlikely by the reporter.

An 88-year-old male patient died during a study. He had stopped the betahistine 8 days before a myocardial infarction and 19 days before he died. Betahistine was regarded to be unrelated to the adverse event by the reporter and not suspect by the company.

A further case concerned a girl whose mother had received caffeine, dihydroergotamine and betahistine for 10 days during early pregnancy. After an uneventful pregnancy and delivery, the girl was found to be neurologically and mentally retarded at the age of 2.5 years. The GDSS department assessed the role of betahistine as non-suspect. The gynaecologist excluded a causal relationship with the mother's medication. Instead an inherited mitochondrial defect was discussed.

In summary, in the four reported fatal cases, the reporter assessed the causal relationship to betahistine in two as unrelated, in one as unlikely and the other as unassessable. The low reporting rate and the weak causal association between betahistine and fatal outcome underline the good safety profile of the drug.

3.2 Hypersensitivity Reactions

Based on the histaminergic properties of betahistine, the signs and symptoms of hypersensitivity reactions could theoretically occur in response to therapy. Histamine is known to play a crucial rule in the development of the immediate type of an allergic response. Similar phenomena are known from histamine release after consumption of certain foods such as strawberries or tomatoes. Histamine-induced reactions are mostly H_1 and H_2 receptor mediated causing, for example, vasodilation, increased capillary permeability or just itching. Betahistine possesses agonistic properties to the H_1 receptor but with a clear minor affinity compared with histamine,[5] and has nearly no affinity to the H_2 receptor. Signs and symptoms of cutaneous hypersensitivity reactions during betahistine therapy were the most frequently reported complaints. They consisted of usually mild and self-limiting rash, pruritus and urticaria. All symptoms were reversible after drug discontinuation.

Betahistine was reported to be involved in one anaphylactoid reaction and one case of Stevens-Johnson syndrome. Anaphylactic reactions with fatal outcome were not reported. From clinical experience, betahistine can be regarded as having a low sensitising risk.

3.3 Gastrointestinal Disorders

The reports that describe gastrointestinal complaints mostly concern nausea and vomiting or unspecific abdominal pain. These were typically non-serious complaints and were normally met by lowering the dosage or administering betahistine during meals. Betahistine has an extremely weak effect on gastric secretion because of its low H_2 receptor affinity.[6] As the action of betahistine on the H_2

receptor cannot be ruled out, it is advised that special care be taken in patients with a medical hisotry of gastric ulcer.

3.4 Hepatobiliary Disorders

Hepatobiliary involvement was reported 25 times, including elevated liver enzyme levels in general and increases in alkaline phosphatase, γ-glutamyltransferase, alanine and aspartate aminotransferase levels. None of the patients concerned developed severe liver failure or died.

In a recently published paper, De Abajo et al.[31] analysed relevant drug-induced liver injuries using the General Practice Research Database in the UK in a population based on a case-control study. The survey of 15 780 recipients reported one patient who developed a cholestatic injury and one patient with a mixed liver injury during betahistine therapy. The authors assume that both patients received the drug for a prolonged period. No underlying disorders, including pre-existing liver malfunctions, are described, and no concomitant drugs are indicated. The two cases mentioned are not characterised by a typical histological pattern. In view of the large number of patients treated with betahistine since market introduction and the only anecdotal reports of liver injury that have been received, liver impairment seems to be of secondary clinical relevance and was mostly caused by factors other than well guided betahistine therapy.

3.5 Neoplasms

The neoplasm classification includes unspecified neoplasms, including cysts and polyps. A total of three cases of neoplasm have been reported. In two of these cases, one with malignant breast tumours and one with colon tumours, the tumours were thought to not be associated with betahistine therapy. In the third patient, phaeochromocytoma was suspected to explain his weight loss, insomnia, impatience and irritability. Unfortunately, no further information was provided and the reporter did not assess the causal relationship to betahistine.

Betahistine use is not recommended for patients with phaeochromocytoma. The rationale is that histamine may induce catecholamine release directly from the chromaffine granules of the tumour with a marked preference for adrenaline (epinephrine) over noradrenaline. The reaction could be suppressed by an H_1 receptor antagonist.[32] Because of its histaminergic properties, betahistine is supposed to act like an H_1 receptor agonist and is contraindicated in patients with phaeochromocytoma. Theoretically, histamine may provoke hypertensive crisis in patients with phaeochromocytoma. However, clinical observations did not confirm the histamine properties after administration of histamine liberating drugs.[33] The signs and symptoms in the unique case report of a patient with a suspected phaeochromocytoma ADR were rather unspecific and do not strongly support the diagnosis. Unfortunately the case can not be evaluated fully since important information is lacking and follow up efforts were unsuccessful.

3.6 Nervous System and Psychiatric Disorders

The ADRs related to the nervous system predominantly reveal heterogeneous events that are not suggestive of a specific adverse reaction profile for betahistine.

Dizziness or vertigo were reported in 51 patients, and are an indication for betahistine treatment. However, it is not known whether the dizziness and balance disorders seen were adverse events related to betahistine or a manifestation of the vestibular disorder being treated. Histamine may enhance wakefulness, probably mediated by central H_1 receptor action. Insomnia, restlessness, agitation, nervousness or irritability can be anticipated in betahistine treatment. As they are only occasionally reported, these reactions appear to be of minor clinical relevance.

In a randomised comparative study, Schneider et al.[34] confirmed the non-sedating properties of betahistine. Spectral analysis of EEG and the reaction time revealed no alteration under betahistine, the P300 showed only slight effects. None of the 30 volunteers experienced drowsiness. Absence of sedation means that in clinical practice rehabilitation

of patients with vestibular disorders may start without any delay during betahistine therapy.

3.7 Respiratory, Thoracic and Mediastinal Disorders

A clinical intolerance to betahistine that gave rise to asthma or bronchospasm was only reported in eight ADRs. Even considering the reports of patients who complained about dyspnoea (n = 14) or cough (n = 5), the overall reporting frequency is low.

In general practice, histamine inhalation studies may support diagnosis in patients with an irritable respiratory system. Theoretically, inhalation of betahistine solution may induce bronchospasms and a decrease in blood pressure. However, an early toxicology study revealed that a betahistine aerosol did not lead to bronchial constriction during a 15-minute exposure whereas a comparable histamine aerosol induced bronchial constriction within 1 minute.[35] Respiratory problems concern isolated reports and betahistine does not jeopardise patients with a known history of asthma.

3.8 Drug Interactions

Characteristic features of drug interactions with betahistine are not described in the scientific literature. As betahistine is well known as a non-sedating drug and free from psychomotor impairment,[36] an interaction with ethanol appears to be very unlikely.

However, as a result of the betahistine/histamine analogy, an interaction with antihistaminergic agents such as terfenadine or cetirizine could be hypothesised. Based on further theoretical considerations, betahistine could induce or support hypersensitive reactions with regard to the H_1-agonistic quality. A pharmacodynamic interference with antihistaminergic drugs could be suspected, but betahistine affinity at the receptor side is significant weaker than histamine affinity.[5,6] In addition, betahistine-induced histamine release from mast cells is not described.[37] Pharmacokinetic drug interactions are not known at present.[12]

3.9 Overdose

Most of the patients who took a betahistine overdose experienced mild to moderate, unspecific symptoms that were self-limiting. In two cases convulsions were observed: one patient took betahistine 728mg and another overdosed with multiple drugs. A harmful outcome was not reported.

In a double-blind, prospective, randomised, cross-over study, Betts et al.[36] compared the effects of betahistine, prochlorperazine and placebo on driving skills and psychomotor abilities in healthy volunteers. Even dosages of betahistine 216 mg/day revealed no differences in all tests in comparison with placebo. Severe ADRs were not observed in this setting.

3.10 Special Patient Groups

Quantifying ADRs in children, pregnant and lactating women, and the elderly is an important concern of post-authorisation safety surveillance, especially if there is no systematic exposure of these patients in clinical trial settings.

The data on use of betahistine during pregnancy and lactation are insufficient. One ADR report concerned a girl with a partial bilateral syndactyly of the second and third toe. The mother had started betahistine treatment during her third month of pregnancy. In addition, alcohol consumption of the mother was noted. Congenital abnormality with a suspected mitochondriopathy was reported in a second case. A further patient presented with radial limb defects and scoliosis after intrauterine exposure to betahistine. The complex syndrome was diagnosed as VACTERL-association. The reports received are not comprehensive enough to assess possible harmful effects of betahistine therapy during pregnancy or lactation.

There are only anecdotal ADRs reported concerning children or adolescent patients (n = 5) who took betahistine partly by accident. An accurate safety assessment is not possible. In his study, Chistyakova[38] used betahistine in children aged 6 to 14 years who had acute or progressive neurosensory hypoacusis and vestibulopathy. The drug was well

tolerated without any reported problems and adverse effects.

Regarding elderly patients, 163 ADR reports were received, the majority of which (n = 98) were non-serious. The reported signs and symptoms in the geriatric population revealed no particular safety issues that would indicate an altered benefit-risk profile for this age group. A specific dosage regime or route of administration is not required.

Comparable findings concern patients with treatment duration exceeding 12 months. The benefit-risk relationship remains the same as in patients with short-term treatment. Effects of chronic betahistine use on the H_3 receptor plasticity are not completely understood so far and further research is required.[14]

4. Conclusion

More than 35 years of post-authorisation experience with betahistine therapy have led to a well documented safety profile of the compound. Using contemporary drug safety surveillance and data mining techniques, no new safety signals were identified based on an estimated exposure of >130 million patients treated with betahistine. The overall reporting frequency of ADRs to the MAH was remarkable low, yielding an estimated rate of 1 : 100 000. The data derived from post-authorisation surveillance confirm the results of clinical studies and outline the good safety profile of the drug.

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References

1. Sheldon CH, Horton BT. Treatment of Meniere's disease with histamine administered intravenously. Proc Staff Meet Mayo Clin 1940; 15: 17-21
2. Hill SJ, Ganellin CR, Timmerman H, et al. International Union of Pharmacology. XIII. Classification of histamine receptors. Pharmacol Rev 1997; 49: 253-77
3. Liu C, Ma XJ, Jiang X, et al. Cloning and pharmacological characterization of a fourth histamine receptor (H_4) expressed in bone marrow. Mol Pharmacol 2001; 59: 420-6
4. Arrang JM, Garbarg M, Quach TT, et al. Actions of betahistine at histamine receptors in the brain. Eur J Pharmacol 1985; 111: 73-84
5. Ganellin CR. Chemistry structure-activity relationship of drugs acting at histamine receptors. In: Ganellin CP, Parsons ME, editors. Pharmacology of histamine receptors. Bristol: Wright PSG, 1982: 10-102
6. Gater PR, Webber SE, Gui GPH, et al. Some studies of the action of betahistine at H_1 and H_2 receptors for histamine. Agents Actions 1986; 18: 342-50
7. Curwain BP, Holton P, Spencer J. The effect of betahistine on gastric acid secretion and mucosal blood flow in conscious dogs. Br J Pharmacol 1972; 46: 351-4
8. Woodward DF, Ledgard SE. Histamine induced microvascular permeability increases in hamster skin: a response predominantly mediated by H_2-receptors. Agents Actions 1986; 18: 504-7
9. West RE, Zweig A, Shih NY, et al. Identification of two H3-histamine receptor subtypes. Mol Pharmacol 1990; 38: 610-3
10. Laurikainen EL, Miller JM, Nuttall AL. The vascular mechanism of action betahistine in the inner ear of the guinea pig. Eur Arch Otorhinolaryngol 1998; 255: 119-23
11. Dziadziola JK, Laurikainen EL, Rachel JD. Betahistine increases vestibular blood flow. Otolaryngol Head Neck Surg 1999; 120: 400-5
12. Soto E, Chávez H, Valli P, et al. Betahistine produces postsynaptic inhibition of the excitability of the primary neurons in the vestibular endorgans. Acta Otolaryngol Suppl 2001; 545: 19-24
13. Lacour M, Sterkers O. Histamine and betahistine in the treatment of vertigo: elucidation of mechanisms of action. CNS Drugs 2001; 15 (11): 853-70
14. Tighilet B, Trottier S, Mourre C, et al. Betahistine dihydrochloride interaction with the histaminergic system in the cat: neurochemical and molecular mechanisms. Eur J Pharmacol 2002; 20: 63-73
15. Botta L, Mira E, Valli S, et al. Effects of betahistine and of its metabolites on vestibular sensory organs. Acta Otorhinolaryngol Ital 2001; 21 (3 Suppl. 66): 24-30
16. Chen XY, Zhong DF, Duan JL, et al. LC-MS-MS analysis of 2-pyridylacetic acid, a major metabolite of betahistine: application to a pharmacokinetic study in healthy volunteers. Xenobiotica 2003; 33: 1261-71
17. Reilly MA, Schayer RW. Further studies on histamine catabolism in vivo. Br J Pharmacol 1971; 43: 349-58
18. Colletti V. Medical treatment in Meniere's disease: avoiding vestibular neurectomy and facilitating postoperative compensation. Acta Otolaryngol 2000, Suppl. 544: 27-33
19. Mira E, Guidetti G, Ghilardi PL, et al. Betahistine dihydrochloride in the treatment of peripheral vestibular vertigo. Eur Arch Otorhinolaryngol 2003 Feb; 260 (2): 73-7. Epub 2002 Sep 11
20. Albera R, Ciuffolotti R, Di Cicco M, et al. Double-blind, randomized, multicentre study comparing the effect of betahistine and fluranizine on the Dizziness Handicap in patients with recurrent vestibular vertigo. Acta Otolaryngol 2003, 260: 73-7
21. Gordon CR, Shupak A. Prevention and treatment of motion sickness in children. CNS Drugs 1999, 12: 369-81
22. Chistyakova VR. The role of betaserk in combined treatment of neurosensory hypoacusis and vestibulopathy in childhood. Bulletin of otorhinolaryngology 2004, 2: 9-12

23. Code of Federal Regulations. Title 21, Chapter 1. Food and Drug Administration, Department of Health and Human Services. Part 312.32. IND Safety Reports: revised 1 April 2002

24. WHO Collaborating Centre for Drug Statistics Methodology [online]. About the ATC/DDD system. Available from URL: http://www.whocc.no/atcddd/atcsystem.html [Accessed 2006 Mar 18]

25. Beeley L, Cunningham H, Brennan A. Betahistine and terfenadine. In: Stockley IH. Drug interactions. 5th Ed. London: Pharmaceutical Press, 2000: 779

26. CIOMS. Guidelines for preparing core clinical safety information on drugs. Report from CIOMS working group III. Genf WHO, 1995

27. Wilson AM, Thabane L, Holbrook A. Application of data mining techniques in pharmacovigilance. Br J Clin Pharmacol 2003; 57: 127-34

28. Biriell C, Edwards R. Reasons for reporting adverse drug reactions: some thoughts based on an international review. Pharmacoepidemiol Drug Saf 1997; 6: 21-6

29. ICH Harmonised Tripartite Guideline. Clinical safety data management: definitions and standards for expedited reporting E2A [online]. Available from URL: http://www.ich.org/LOB/media/MEDIA436.pdf [Acessed 2006 Mar 18]

30. Davies AG, Stonier PD. Development of medicines: full development. In: Griffin JP, O'Grady J, editors. The textbook of pharmaceutical medicine. London: BMJ, 2003: 395-420

31. de Abajo FJ, Montero D, Madurga M, et al. Acute and clinically relevant drug-induced liver injury: a population based case-control study. Br J Clin Pharmacol 2004; 58: 71-80

32. Dendorfer A, Fitschen M, Raasch W, et al. Mechanisms of bradykynin-induced catecholamine release in pithed spontaneously hypertensive rats. Immunopharmacology 1999; 44: 99-104

33. Prys-Roberts C. Phaeochromocytoma: recent progress in its management. Br J Anaesth 2000; 85: 44-57

34. Schneider D, Kieβling B, Wieczorek M, et al. Influence of 3 antivertiginous medications on the vigilance of healthy volunteers. Int J Clin Pharmacol Ther 2003; 41: 171-81

35. Waggoner WC. Pharmacology and toxicology of Serc (betahistine hydrochloride). Report Unimed Inc Feb. 1970

36. Betts T, Harris D, Gadd E. The effect of two anti-vertigo drugs (betahistine and prochlorperazine) on driving skills. Br J Pharmacol 1991; 32: 455-8

37. Kohno S, Nakao S, Ogawa K, et al. Possible participation of histamine H3-receptors in the regulation of anaphylactic histamine release from isolated rat peritoneal mast cells. Jpn J Pharmacol 1994; 66: 173-80

38. Chistyakova VR. The role of betaserk in combined treatment of neurosensory hypoacusis and vestibulopathy in childhood. Vestn Otorinolaringol 2004; 2: 9-12

Correspondence and offprints: Dr *Sabine Jeck-Thole*, Solvay Pharmaceuticals, Hans-Böckler-Allee 20, Hannover, 30172, Germany.
E-mail: sabine.jeck-thole@solvay.com