Lareb

Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

Antipsychotic drugs and hypothermia

Introduction

Antipsychotic drugs (APDs) have been approved for the Dutch market mainly for the treatment of *psychotic episodes*. The group of APDs is diverse, and consists of the classic antipsychotic drugs, such as haloperidol and pipamperon and the atypical antipsychotics, such as aripiprazole, risperidone, and olanzapine.

Reports

Up to March 11, 2008 the Netherlands Pharmacovigilance Centre Lareb received 16 reports of hypothermia in association with an APD. In six reports pipamperon was the suspect drug, in six reports risperidone was the suspect drug.

Table 1. reports of hypothermia in association with antipsychotic drug use.

patient, Sex, age	drug Indication for use	concomitant medication	suspected adverse drug reaction	time to onset, outcome
A F, 86 14400	pipamperon nocturnal restlessness	haloperidol furosemide	hypothermia (33.7 ^{0}C)	some hours positive dechallenge
B V, 90 14401	pipamperon restlessness, confusion	furosemide carbasalate calcium temazepam	hypothermia (32.1 ^{0}C)	some hours positive dechallenge
C V, 84 14402	pipamperon restlessness, delusions	not reported	twice hypothermia (<34 ^{0}C and 33.1^{0}C)	some hours positive dechallenge
D V, 78 16981	pipamperon 40 mg OD not reported	oxazepam	hypothermia	3 weeks not reported
E V, 90 18038	pipamperon 40 mg BID restlessness	colecalciferol calcium ferrous fumarate oxazepam paracetamol	hypothermia	10 months positive dechallenge
F V, 49 23038	olanzapine conversion disorder		walking disorder stomach pain vomiting, anuria sedation, decreased consciousness communication disorder, erythema paraesthesia in legs thyroid function disorder liver function disorder hypoalbiminuria thrombocytopenia and haematuria, hypothermic	not reported not reported
G (27398) V, 87	risperidone 1 mg BID anxiety and restlessness	magnesium hydroxide oxazepam paracetamol	hypothermia (33 ^{0}C)	1 year patient died ten days later, relation with reported ADR unclear
H	quetiapine 400 mg BID	valproic acid	hypothermia (31 ^{0}C)	16 weeks

patient, Sex, age	drug Indication for use	concomitant medication	suspected adverse drug reaction	time to onset, outcome
V, 62 40711	not reported	venlafaxine		positive dechallenge
I M, 41 43008	risperidone 8 mg/day schizophrenia with psychotic decompensation	not reported	hypothermia (29.7 ^{0}C) drowsiness dyspnoea	1 day recovered after treatment in hospital
J M, 45 43009	levomepromazine behavioural disorder	not reported	hypothermia (32 ^{0}C) drowsiness	not reported recovered
K V, 82 55106	risperidone 4 mg/day not reported	perphenazine	hypothermia (33 ^{0}C) increased hallucinations	not reported not recovered
L V, 51 55285	risperidone Consta 37.5 mg per 14 days schizoaffective psychosis	penfluridol lithium carbonate tranylcypromine sulphate oxazepam levothyroxine lormetazepam psyllium hydrophilic mucilloid	hypothermia (30 ^{0}C)	3 months not recovered on ongoing risperidone therapy
M M, 8th decade 56858	risperidone Consta 37.5 mg not reported	not reported	hypothermia (34 ^{0}C) pancytopenia hyponatremia drowsiness orthostasis	not reported not reported
N V, 59 61363	pipamperon not reported valproic acid not reported	haloperidol omeprazole	hypothermia (33 ^{0}C) thrombopenia acute renal failure drowsiness	not reported recovered 48 hours after cessation of pipamperon
O M, 41 62177	aripiprazole 15 mg OD schizophrenia	perphenazine	hypothermia	3 days recovered within one week after cessation
P V, 62 74215	quetiapine 500 mg/day late onset schizophrenia	telmisartan atorvastatin spirinolacton temazepam lorazepam	hypothermia	5 days after dose increase from 200 mg/day to 500 mg/day recovered on ongoing therapy after treatment

The reports concerning patients A, B and C are from the same reporter. Reports F, H, K and L originate from MAHs. Patients I and J were published in the Nederlands Tijdschrift voor Geneeskunde (NTvG) [1]. If reported, the exact body temperature is listed in the Table.

Other sources of information

Literature

In a recent publication Van Marum *et al*. found 32 publications containing 43 case reports concerning hypothermia during APD use. In these case reports APD use was not

associated with a specific age group. Reported ages varied from 0 to 90 years. In most cases, hypothermia was detected shortly following the start or dose increase of an antipsychotic drug. Most patients suffered from schizophrenia [2].

Databases

In January 2008 the Lareb database contained 54 reports on hypothermia, 2067 reports on the APDs. The reporting odds ratio is 13.5 (95%CI 7.5-24.2).
A search in the WHO database for reports of hypothermia and APD use (ATC-code N05A, with exclusion of lithium) revealed 480 reports of patients developing hypothermia during the use of APDs. The results for the various APDs are shown in the study performed by Van Marum *et al*. [2].
Based on the reports, no specific pharmacological subgroup could be associated with an increased risk for hypothermia. New antipsychotic drugs were responsible for 55% of the reports, but this was mainly attributable to risperidone. Risperidone alone was responsible for 27% of all reports. A remarkable high association was found for pipamperone (ROR: 24.6; 95%CI 13.2–46.1), an antipsychotic drug mainly used in Europe [2].

Mechanism

Hypothermia associated with APD use seems to have several possible causes. Van Marum *et al.* describe the following hypotheses [2].
First, drug-receptor profile may play a role. Serotonin is associated with thermoregulation. In the case reports and in the WHO database APDs with a stronger affinity for the 5-HT_{2a} receptor than for the D_2-receptor, i.e. pipamperone and the atypical APDs, are associated with hypothermia.
Alpha2-adrenergic receptors are also involved in thermoregulation, by inducing peripheral responses to cooling (vasoconstriction and shivering). Blocking of this receptor, by e.g. chloropromazine, risperidone, clozapine, or thioridazine, will inhibit these peripheral responses and lead to hypothermia
Second, patient factors must be taken into account. The pre-optic anterior hypothalamic region regulates body temperature. Patients with pre-existing brain damage may be more susceptible to hypothermic effects.
Third, ambient temperature plays a role in thermoregulation. In animal studies, APD administration at ambient temperatures below 22°C led to hypothermia, whereas APD administration in a room temperature of 29°C gave no thermal response and at 32°C an increase in rectal temperature was found [3]. Furthermore, a cold environment will normally lead to behaviour aimed at protection against the cold, like putting on extra clothes. APDs, however, induce apathy and indifference by dopamine blockage, the patient won't be aware of the cold or won't protect him self against it.
Finally, since some case reports also mentioned the co-existence of infections at the time of development of hypothermia, this might also play a role in the deregulation of thermal homeostasis [2].

Discussion and conclusion

The reports received by Lareb and the WHO, the case reports found in literature and the possible mechanism support the association between hypothermia and APD use. Hypothermia is a serious and unpredictable event, frequently leading to hospital and ICU admission and sometimes even to death. Some authors have even suggested that a substantial proportion of unexplained deaths should be attributed to antipsychotic-induced hypothermia [2].
The high association for relatively new drugs, like the atypical APDs, can partially be explained by reporting bias, but the high number of reports for risperidone should keep clinicians alert.

Considering all this, it is suggested that hypothermia should be mentioned in the SmPC of every APD.

References

1. van Marum RJ, Jansen S, Ponssen HH. Antipsychotica als oorzaak van diepe hypothermie. Ned Tijdschr Geneeskd 2003;147(25):1201-4.
2. van Marum RJ, Wegewijs MA, Loonen AJ, Beers E. Hypothermia following antipsychotic drug use. Eur J Clin Pharmacol 2007;63(6):627-31.
3. Sharma RP, Janicak PG, Bissette G, Nemeroff CB. CSF neurotensin concentrations and antipsychotic treatment in schizophrenia and schizoaffective disorder. Am J Psychiatry 1997;154(7):1019-21.

This signal has been raised on June 2008. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbg-meb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).