Angiotensin II Receptor Antagonists – An Assessment of their Toxicity

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Objective

The aim of the study was to assess the toxicity of angiotensin II receptor antagonists in overdose, because there is little information in the literature on this topic.

Methods

In a retrospective study, cases of exposure to angiotensin II receptor antagonists from seven Poisons Information Centres in Austria, Germany, and Switzerland were analysed. Inclusion criteria were monointoxication, defined dose, and documented follow-up. Severity of poisoning was assessed according to the Poisoning Severity Score (PSS).

Case series

Patients and dose

In total, 206 cases of exposure to angiotensin II receptor antagonists were registered (Table 1). Patients involved were 150 children (0.8 – 13 years) and 56 adolescents (15 – 17 years) or adults (28 – 77 years). Dose expressed as a multiple of the maximum daily dose for adults (MDD) ranged between 0.06 – 6.5 (median 0.5) in children and 0.5 – 50 (median 7.8) in adolescents/adults.

Table 1: Cases of exposure to angiotensin II receptor antagonists

Drug	Number of cases	Age (years) median (range)	Dose (mg) median (range)	Dose (multiple of MDD) median (range)	MDD (mg)
Candesartan	94	2.4 (0.8 – 71)	16 (2 – 960)	0.5 (0.0625 – 30)	32
Eprosartan	3	2.3 (1.6 – 17)	300 (300 – 12000)	0.5 (0.5 – 20)	600
Irbesartan	20	4 (1 – 72)	262 (75 – 15000)	0.875 (0.25 – 50)	300
Losartan	26	3 (0.9 – 67)	50 (6.25 – 2600)	0.5 (0.0625 – 26)	100
Olmesartan	16	4.5 (1.3 – 69)	25 (10 – 640)	0.625 (0.25 – 16)	40
Telmisartan	18	2.7 (1.8 – 73)	80 (20 – 2400)	1 (0.25 – 30)	80
Valsartan	29	5 (0.9 – 77)	160 (20 – 8000)	0.5 (0.0625 – 25)	320

Symptoms and severity

Most children remained asymptomatic (82.7 %), 16.7 % developed mild symptoms (Fig.1a). Only in one case, hypotension required therapeutic measures after ingestion of the 1.5-fold maximum dose of candesartan by a 2.5-year-old toddler. In adolescents/adults almost half of the patients suffered from mild (37.5 %) or moderate symptoms (8.9 %) (Fig.1b).

Table 2: Symptoms caused by poisoning with angiotensin II receptor antagonists (n = number of symptomatic cases)

Symptom	Children (n = 26)	Adolescents/Adults (n = 26)
Hypotension	54	42
Fatigue	19	19
Dizziness	3,8	19
Nausea/Vomiting	7,7	23
Somnolence	7,7	12
Collapse		7,7
Tachycardia	3,8	7,7
Sensation of cold		3,8
Coma		3,8
Bradycardia		3,8
Palpitations		3,8
Dyspnoea	3,8	3,8
Diarrhoea		3,8
Drowsiness	3,8	
Apathy	3,8	
Abdominal pain	7,7	
Asthenia	3,8	
Hyperthermia (mild)	3,8	
Pallor	3,8	

The most frequent symptoms were hypotension (48 %, usually mild), fatigue (19 %), nausea/vomiting (15 %), dizziness (12 %), and somnolence (10 %) (Table 2). In moderate poisonings, collapse, coma or pronounced hypotension were observed in adults after ingestion of a 5 - 7-fold maximum dose of valsartan or a 20 – 50-fold maximum dose of eprosartan, irbesartan or telmisartan. There were no severe poisonings.

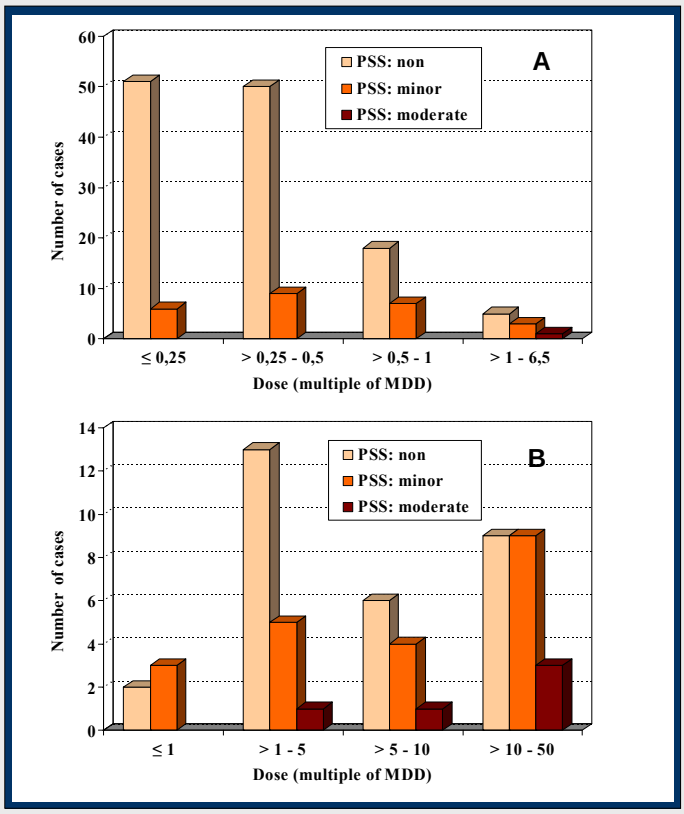

Fig. 1: Doses ingested and severity of poisonings (PSS) caused by angiotensin II receptor antagonists in children (A) and adolescents/adults (B)

Conclusions

After ingestion of the maximum daily dose for adults by children, there is no or only mild toxicity. Higher doses may cause moderate poisoning requiring appropriate treatment. In adults, doses from the 5-fold maximum daily dose may induce moderate toxicity. In general, angiotensin II receptor antagonists seem to have a wide therapeutic index. Differences in toxicity within the group of angiotensin II receptor antagonists can not be assessed in this study because the number of cases for most substances was too small.