

Prednisolone and hiccups

Introduction

Prednisolone is a corticosteroid drug with predominant glucocorticoid and low mineralocorticoid activity which is used to treat a variety of inflammatory and auto-immune condition [1]. Prednisolone has been marketed internationally since 1955. Prednisolone is the active metabolite of the drug prednisone and is preferred especially in patients with hepatic failure, as these individuals are unable to metabolise prednisone into prednisolone [2].

Prednisolone irreversibly binds with glucocorticoid receptors (GR) alpha and beta for which they have a high affinity. AlphaGR and BetaGR are found in virtually all tissues with variable numbers between 3000 and 10000 per cell, depending on the tissue involved. Prednisolone can activate and influence biochemical behaviour of most cells. The steroid/receptor complexes dimerise and interact with cellular DNA in the nucleus, binding to steroid-response elements and modifying gene transcription. They induce synthesis of some proteins, and inhibit synthesis of others [3].

A hiccup is an involuntary, intermittent, spasmodic contraction of the diaphragm and intercostal muscles. There are numerous causes of hiccups. Hiccups are usually caused by gastric distention from overeating or carbonated beverages. Other causes include gastrointestinal disorders, thoracic disorders or cardiac disorders. Hiccups may also be drug-related. In rare cases, hiccups can be a manifestation of severe underlying disease (eg, malignancy, multiple sclerosis) [4].

Reports

The Netherlands Pharmacovigilance Centre Lareb received 3 reports of hiccups associated with the use of prednisolone, in a period from July 11th 2013 to November 1st 2013.

Case A (157126)

This non-serious spontaneous report from a pharmacist concerns a male aged 71 years and older, with hiccups following administration of prednisolone tablets 20 mg twice daily for asthma with a latency of 1 day after start. The hiccups lasted for 4 days. Prednisolone was withdrawn. The patient recovered. Concomitant medications were levothyroxine sodium, salbutamol/ipratropium, salmeterol/fluticasone, alfacalcidol, fenoterol/ipratropium, tiotropium bromide, formoterol/beclometasone, indacaterol, montelukast, pravastatin, candesartan, diltiazem, carbasalate calcium, pantoprazole, lercanidipine. Start- and stopdates of the concomitant medications were not reported, follow-up questions did not lead to more information.

Case B (160866)

This report from a pharmacist concerns a male aged 61-70 years years, with hiccups following administration of prednisolone capsules 30 mg once daily for exacerbation of a lung disease and pregabalin 150 mg twice daily for neuropathic pain with a latency of 2 days after start of prednisolone and 1 year after start of pregabalin. The dose for prednisolone and pregabalin was not changed. The patient recovered after 5 days. Concomitant medications were

formoterol/budesonide, alfuzosin, amlodipine, metformin, omeprazole and allopurinol.

Follow-up questions about the duration of treatment with prednisolone did not lead to more information.

Case C (162118)

This non-serious spontaneous report from a specialist doctor concerns a male of unknown age, with hiccups following oral administration of prednisolone (dose unknown) for Bechterew's disease with a latency of 1 day after start. The drug prednisolone was withdrawn. The patient recovered almost immediately. After restart of intramuscular prednisolone some time later, the hiccups appeared again within 24 hours. After withdrawal the patient recovered. Concomitant medication was not reported.

Other sources of information

SmPC

Hiccups are not mentioned in the SmPC of prednisolone [5], however the SmPC's of dexamethasone [6], betamethasone [7] and methylprednisolone [8] do mention hiccups.

Literature

Although not widely reported, several articles associate hiccups with corticosteroid treatment, however not specifically with prednisolone. Peacock [9] describes a patient who was given preoperative dexamethasone and developed hiccups before anaesthesia and surgery commenced. He at no time was in distress, and the surgical procedure was completed without complication. By the second postsurgical day his hiccups were resolved completely. Other authors report annoying hiccups following intra-articular corticosteroid injection of betamethasone acetate/betamethasone sodium phosphate at the knee joint [10]. A case series presents five patients who developed hiccups after receiving dexamethasone for chemotherapy-induced nausea and vomiting. However, switching dexamethasone to an equipotent dosage of either methylprednisolone or prednisolone resolved the hiccups [11]. This was also seen in a study of 40 cancer patients. Dexamethasone-induced hiccups in these patients could be controlled by replacing dexamethasone with methylprednisolone. After readministration of dexamethasone 74% had recurrence of hiccups [12].

Databases

On April 4th 2014, the database of the Netherlands Pharmacovigilance Centre Lareb contained 3 reports of hiccups associated with the use of prednisolone. Hiccups might possibly be a class-effect of corticosteroids, therefore other corticosteroids were taken into account as well.

Table 1. Reports of hiccups associated with the use of glucocorticoids in the Lareb, WHO and Eudravigilance database [13,14].

Database	Drug	Number of reports	ROR (95% CI)
Lareb	Prednisolone	3	5.9 (1.9-18.7)
	Betamethasone	1	N.A.
	Dexamethasone	10	42.9 (22.2-82.8)
	Methylprednisolone	2	N.A.
WHO	Prednisolone	27	3.0 (2.0-4.3)
	Betamethasone	50	26.1 (19.7-34.6)
	Cortisone	2	N.A.
	Dexamethasone	268	30.5 (27.0-34.6)
	Hydrocortisone	7	2.8 (1.4-6.0)
	Methylprednisolone	48	6.2 (4.6-8.2)
	Prednisone	17	1.4 (0.9-2.3)
	Triamcinolone	12	3.3 (1.9-5.8)
	Eudravigilance	Prednisolone	7
Betamethasone		10	12.1 (6.5 – 22.6)
Cortisone		2	N.A.
Dexamethasone		38	11.2 (8.1 – 15.4)
Hydrocortisone		1	N.A.
Methylprednisolone		11	3.5 (1.9 – 6.4)
Prednisone		4	0.8 (0.3 – 2.2)
Triamcinolone		2	N.A.

Prescription data

Table 3. Number of patients using glucocorticoids (with ATC code H) in the Netherlands between 2009 and 2013 [15].

Drug	2009	2010	2011	2012	2013
Prednisolone	412,080	427,550	452,730	472,340	488,330
Betamethasone	31,541	34,069	18,280	20,007	23,803
Cortisone	2,269	2,181	1,787	1,475	1,385
Dexamethasone	34,918	35,015	46,520	42,169	44,692
Hydrocortisone	6,502	7,235	8,024	7,984	8,611
Methylprednisolone	11,615	11,831	11,913	11,589	11,832
Prednisone	39,707	34,979	33,030	29,778	25,635
Triamcinolone	170,910	173,930	179,380	182,940	190,310

Mechanism

The mechanism by which corticosteroids induce hiccups has not been fully elucidated yet. Hiccups have been classified as a neurologic reaction triggered by a multitude of factors. However, it has been proposed that corticosteroids lower the threshold for synaptic transmission in the midbrain and directly stimulate the hiccup reflex arc [16].

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 3 reports of hiccups associated with the use of prednisolone. Two positive dechallenges and one positive rechallenge were reported.

The association of prednisolone and hiccups is supported by a statistically significant disproportionality in the database of Lareb and the WHO. This is also the case for other glucocorticoids. The literature mentions hiccups predominantly with the use of dexamethasone and corticosteroid rotation with (methyl)prednisolone is thought to reduce the hiccups. The mechanism behind this is not clear. Other glucocorticoids such as betamethasone are also described to induce hiccups. Therefore, the more potent corticosteroids are reported in the literature to induce hiccups. Possibly the relatively high doses of prednisolone administered in the patients described in the cases reported to Lareb contribute to the occurrence of the hiccups. Several SmPCs of glucocorticoids already mention hiccups as an adverse event, however the SmPC of prednisolone does not.

- Hiccups should be mentioned in the SmPC of prednisolone

References

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This signal has been raised on October 2014. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbqmeb.nl/cbq/en/default.htm