

Propranolol and weight gain

Introduction

Propranolol is a strong lipophilic drug that belongs to the class of non-selective β -blockers. It inhibits all three β -adrenergic receptors, but its affinity for the β_1 - and β_2 -receptors is 100-fold higher compared to β_3 -receptors [1].

Propranolol has been granted marketing authorization in the Netherlands since June 1983. The drug is indicated for the treatment of *angina pectoris*, *hypertension*, *prophylactic treatment after a myocardial infarction*, *hypertrophic obstructive cardiomyopathy*, *tremor simplex*, *supraventricular and ventricular arrhythmia*, *hyperthyroidism and thyrotoxicosis*, *pheochromocytoma*, *migraine* and *prophylaxis of bleeding in the upper part of the gastro-intestinal tract in patients with portal hypertension and varices at the height of the oesophagus* [2].

Several drugs are known to cause changes in body weight. Weight gain is the consequence of energy imbalance, when energy intake exceeds energy expenditure over a prolonged period of time. Drug-induced weight gain can arise as a consequence of differing mechanism, such as increased appetite, fluid retention or reduced metabolism [3].

Reports

In the period from October 1st 1987 until July 9th 2014, the database of the Netherlands Pharmacovigilance Centre Lareb contained ten reports of weight gain associated with the use of propranolol, see Table 1.

For most patients the weight gain was noticed a few months after start of propranolol. In patient A, the time to onset of 3 hours after start is probably for the insomnia. Time to onset for the weight gain was not specific reported. The number of kg weight gain was reported for 6 patients (B,C,E,G,I,J) and varied from 2 to 16 kg with an average of 9 kg (\pm 5 kg). One patient (I) had a positive de- and rechallenge.

In several patients (A,C,D,E,F) other factors like concomitant medication might be an alternative cause for the weight gain. Patient A also used ethinylestradiol/lynestrenol. In patient C paroxetine was started 1 month after propranolol. For patient F, quetiapine was also reported as suspected drug. For these drugs weight gain is mentioned in the SmPC [4-6].

Patients D and E also experienced fatigue. This may have influenced the weight gain as a result of reduced mobility.

Table 1. Reports of increased weight associated with the use of propranolol

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 3860 F, 41-50 General Practitioner	propranolol tablet 80mg migraine	ethinylestradiol/ lynestrenol	weight gain, insomnia	immediately after 3 hours unknown not reported
B 6464 F, unknown	propranolol capsule 80mg		weight gain (2kg), breast	not reported no change

General Practitioner received through the MAH	migraine		enlargement	not reported
C 24955 M, 21-30 Pharmacist	propranolol tablet 10mg vegetative dystonia	paroxetine	weight gain (13kg)	2 months propranolol unknown, paroxetine withdrawn not reported
D 51019 F, 61-70 Consumer	propranolol tablet 10mg migraine		weight gain, fatigue	4 weeks discontinued not recovered
E 79007 F, 41-50 General Practitioner	propranolol capsule 80mg pain	ethinylestradiol/ levonorgestrel, diclofenac	weight gain (8kg), fatigue	7 months discontinued unknown
F 108244 M, unknown Consumer	quetiapine tablet 25mg, oxazepam, propranolol	venlafaxine, sertraline	headache, weight gain, suicidal ideation, sleeplessness, violent thoughts, irritability, nausea, libido decreased, aggression	not reported unknown unknown
G 118511 F, 41-50 Consumer	propranolol 40 mg tablet hypertension		weight gain (16kg)	a few months discontinued unknown
H 122113 F, 51-60 Pharmacist	propranolol tablet 80mg migraine	eletriptan	weight gain	2 months no change not recovered
I 134480 F, 31-40 Consumer	propranolol 80 mg tablet migraine		weight gain (6kg)	2 weeks discontinued recovered
J 167802 F, 61-70 Consumer	propranolol 80 mg tablet tremor of hands	solifenacine	weight gain (10kg)	months no change not recovered

In patient D the weight gain was treated with levothyroxine. It is not known if this patient had thyroid dysfunction.

Patient H is known with obesity. Her weight was stable until administration of propranolol. There were no changes in her diet that could explain the weight gain. Patient I experienced 6 kg weight gain after administration of propranolol. After withdrawal she lost 5 kg. During prior use of propranolol she experienced 12 kg weight gain. Several diets were not effective. After withdrawal of propranolol she lost 13 kg.

Other sources of information

SmPC

Weight gain is not mentioned in the SmPC of propranolol [2]. It is mentioned in the SmPC of carvedilol PCH [7]. In the SmPC of the other non-selective β -blockers, namely labetalol, sotalol and pindolol, weight gain is not described [8-10]. Weight gain is described in the SmPC of the selective β -blocker metoprolol [11]

Literature

A retrospective analysis of data from a randomized, placebo-controlled, double-blind clinical trial revealed weight gain following administration of propranolol. An increase in weight from baseline was reported in both the propranolol and placebo groups following one year of treatment. The mean weight of patients administered propranolol increased from 78.2 kg to 80.5 kg (+2,3kg) compared with an increase from 77.9 to 79.1 kg (+1,2 kg) in the placebo group (mean difference of 1.2 kg; 95%CI: 0.9-1.5). At the first annual follow-up visit 27% (456/1679) of patients taking propranolol and 21% (350/1648) taking placebo gained more than 5kg in weight. The weight continued to increase during the second year of treatment (mean weight gain 3 kg and 1.6 kg, respectively) [12].

Weight gain was also reported in a study of headache prophylactic therapy. In total, 13 patients were treated with propranolol for 6 months. One patient experienced weight gain (6kg) [13].

Diener et al. conducted a double-blind, placebo-controlled trial to explore the efficacy of topiramate. Propranolol was used as an active control. In the 143 patients with migraine who received propranolol 160 mg/day, 2.3% had an increase in body weight compared to 0.6% in placebo ($p = 0.025$) [14]. A case of a weight gain (9 kg) was reported in a woman who received 9 months of treatment with propranolol 80 mg for migraine prevention [15].

Weight gain is described for β -blockers in general [16-19]. *Sharma et al.* conducted a systematic analysis of β -adrenergic receptor and weight gain, including eight evaluable prospective randomized controlled trials [17]. Their analysis suggested that β -blockers were associated with an initial weight gain during the first few months. The median difference in body weight was 1.2 kg (range -0.4 – 3.5kg). *Belanger et al.* use a randomized controlled trial to determine if resting metabolic rate (RMR) of overweight and sedentary subjects consuming β -blockers can be increased following an aerobic exercise training program. Their results suggest that β -blockers limit the increase in resting metabolic rate. Consequently, obtaining a negative energy balance in an attempt to lose weight may be more difficult [18]. *Gondoni et al.* conducted a randomized controlled trial and found an effect on weight gain for selective but not for non-selective β -blockers [19].

Databases

Table 2. Number of reported cases of weight gain associated with the use of propranolol in the database of Lareb [20], the WHO [21] and Eudravigilance [22].

Drug	Number of reports	ROR (95% CI)
Propranolol	Lareb: 10	4.1 (2.2-7.7)
	WHO: 99	0.9 (0.8-1.1)
	Eudravigilance: 39	1.5 (1.1-2.1)

Prescription data

Table 3. Number of patients using propranolol in the Netherlands between 2009 and 2013 [23].

	2009	2010	2011	2012	2013
Propranolol	119,350	119,780	121,030	119,270	120,180

Mechanism

The exact mechanism how propranolol can cause weight gain is not known. The effect on body weight may partly be explained by changes in energy metabolism, for instance through reduction in: resting energy expenditure, the thermic effect of food, exercise tolerance, tiredness, non-exercise thermogenesis. Further inhibition of lipolysis and exacerbation of insulin resistance may play a role [17].

Propranolol is a non-selective β -receptor blocking agent. $\beta_{1,2}$ and β_3 -receptors are expressed in brown adipose tissue (BAT). Thermogenesis is a key function of BAT, and consists of the generation of heat after exposure to cold or to large energy intake from diet. Studies demonstrated that triple β -receptor knock-out mice have increased susceptibility to cold-induced hypothermia as well as diet-induced, leading to cold intolerance and obesity [24]. The relative contribution of each β -receptor is however less understood.

Propranolol might exert its effect on bodyweight through blockade of β_3 -receptors [25]. Studies demonstrated that adaptive thermogenesis in rodents is induced through β_3 -receptors [26]. However, a study by *Ueta et al.* also demonstrated a major role of the β_1 -receptor in the sympathetic stimulation of BAT thermogenesis in response to cold exposure and high-fat feeding [24].

In mice, propranolol had no effect on body temperature [27]. Stimulation of BAT with a selective β_3 -receptor agonist in mice can however reduce weight gain secondary to high food intake [26,28]. Theoretically, β_3 -receptor blockage may induce weight gain.

Class effect

Weight gain is not described in the SmPC of other non-selective β -blockers [7-10]. The database of Lareb only contains five reports of an increased weight associated with the use of sotalol.

For the selective β -blockers the database of Lareb contains reports for atenolol (5), bisoprolol (7), metoprolol (32) and nebivolol (2). Weight gain is only described in the SmPC of the selective β -blocker metoprolol [11,29-33].

Since the exact mechanism of propranolol-induced weight gain is not known, a possible class effect for selective as well as non-selective β -blockers cannot be excluded.

Discussion and conclusion

Lareb received ten reports of weight gain (average of 9 kg; \pm 5 kg) associated with the use of propranolol. For most patients the weight gain was noticed a few months after start of propranolol. In several patients other factors like concomitant medication might be an alternative cause for the weight gain.

For β -blockers in general, weight gain has been described in literature [11,16,17]. Overall, these drugs are used for the treatment of cardiovascular diseases. In half of the presented cases, propranolol was used for an indication other than cardiovascular diseases, for example migraine. From literature it is known that people with obesity have an increased risk for the development of migraine. However, migraine was not found to increase the risk for weight gain [34,35]. In cases where the propranolol is used for migraine, recovery of the migraine might lead to a higher intake of food.

There were several studies found in literature that support this association. It is disproportionately present in the database of Lareb and Eudravigilance, but not in the database of the World Health Organization. Although the exact mechanism of how propranolol causes weight gain is unknown, there are several possible mechanisms that (together) might explain the weight gain.

- Further investigation of the information of the marketing authorization holders and other national centers is needed to confirm the signal.

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This signal has been raised on November 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