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ORIGINAL PAPER

Rebound acid hypersecretion after withdrawal of gastric acid suppressing drugs: new evidence of similitude

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Background: **Homeopathy is based on the principle of similitude (*similia similibus curentur*) using medicines that cause effects similar to the symptoms of disease in order to stimulate the reaction of the organism. Such vital, homeostatic or paradoxical reaction of the organism is closely related to rebound effect of drugs.**
Method: **Review of the literature concerning the rebound effects of drugs used to suppress gastric acidity, particularly proton pump inhibitors (PPIs).**
Results: **The mechanism of action of these effects is discussed. Rebound in terms of clinical symptoms and physiological effects occur in about 40% of people taking PPIs, their timing depends on the half-life of the drug and the adaptation period of the physiological mechanisms involved. The wide use of PPIs may be linked to the rising incidence of carcinoid tumours.**
Conclusions: **These findings support Hahnemann's concept of secondary action of drugs. We are developing a homeopathic materia medica and repertory of modern drugs on the basis of reported rebound effects.** *Homeopathy* (2011) **100**, 148–156.

Keywords: Homeopathy; Similitude; Secondary effect; Rebound effect; Paradoxical reaction; Withdrawal syndrome; Proton pump inhibitor

Introduction

After conceiving the principle of 'like cures like', Hahnemann sought confirmation by studying existing clinical reports. He found many references that eventually led him to raise the principle of similitude to the level of a 'natural law' supported by inductive logic: for a substance to heal definite symptoms in ill human beings it must elicit similar symptoms upon healthy experimental subjects.

In the seminal work of homeopathy (Essay on a new principle for ascertaining the curative powers of drugs, 1796),[1] Hahnemann systematized the principle of similitude, describing the pharmacological properties of a several drugs commonly used at that time, which had a direct primary action of causing organic disturbances in large doses, and the indirect secondary action of cure of the same disorders in smaller doses.

For instance: "*...We should endeavor to find out if the millefoil (Achillea millefolium) cannot itself produce hemorrhages in large doses, as it is so efficacious in moderate doses in chronic hemorrhages.*[...] *The bear's berry (Arbutus uva ursi) has actually, without possessing any acridity perceptible to the senses, not infrequently increased the difficulty of passing water, and the involuntary flow of urine, by some power peculiar to itself; thereby showing that it has a tendency to produce such affections, and hence, as experience also testifies, it is capable of curing similar disorders in a permanent manner*".[1]

In the introduction of the *Organon*, Hahnemann alludes to homeopathic cures involuntarily achieved by doctors of the 'Old School', giving 247 bibliographic references. For instance: "*If F. Hoffman praises the efficacy of millefoil in various cases of hemorrhage; if G. E. Stahl, Buchwalk and Loseke have found this plan useful in excessive hemorrhoidal flux; if Quarin and the editors of the Bresslauer Sammlungen speak of the cure it has effected of hemoptysis; and finally, if Thomasius has used it successfully in*

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uterine hemorrhage; these cures are evidently owing to the power possessed by the plant, of exciting of itself hemorrhage and hematuria, as observed by G. Hoffman, and more especially of producing epistaxis as confirmed by Boecler. Scovolo among many others, cured a case where the urinary discharge was purulent, by arbutus uva ursi; which never could have been performed if this plant had not the property of exciting heat in the urinary passage with discharge of a mucous urine, as seen by Sauvages".[2]

In paragraphs 56–62 of the *Organon*,[3] Hahnemann describes the enantiopathic method of treatment, mentioning a large number of drugs of his time that were used according to the primary palliative effect to the disturbed symptom, reporting that "*after such short antipathic amelioration, aggravation follows in every case without exception*". Commenting on the alterations that the drugs cause in the health state, in the long and short term, Samuel Hahnemann describes the physiological mechanism of drug action through an immediate 'primary action' of the drug and of a late 'secondary action or counter-action' of the organism.

He mentions several examples of the primary action of the medicines in our organism and the consequent reaction of the vital force (secondary action), which acts in an instinctive way in a sense to preserve the homeostasis or the balance of the internal environment ('life-preserving power'), producing intense and opposite symptoms to the alteration initially induced: "*...Excessive vivacity follows the use of strong coffee (primary action), but sluggishness and drowsiness remain for a long time afterward (reaction, secondary action), if this be not always again removed for a short time by imbibing fresh supplies of coffee (palliative). After the profound stupefied sleep caused by opium (primary action), the following night will be all the more sleepless (reaction, secondary action). After the constipation produced by opium (primary action), diarrhea ensues (secondary action); and after purgation with medicines that irritate the bowels, constipation of several days' duration ensues (secondary action). And in like manner it always happens, after the primary action of a medicine that produces in large doses a great change in the health of a healthy person, that its exact opposite, when, as has been observed, there is actually such a thing, is produced in the secondary action by our vital force*" (paragraph 65).[3]

Hahnemann used the *modus tollens* of deductive Aristotelian logic (the 'null hypothesis' of modern statistics) to evidence the validity of the opposite procedure, the homeopathic use of medicines according to similarity of symptoms (similitude principle).

Observing the iatrogenic effects of allopathic treatment, Hahnemann proposed a therapeutic based on similarity, stimulating the body itself to react (secondary action or vital reaction), administering to the patients substances trigger similar symptoms in the healthy experimenters. In the beginning of the homeopathy, he applied the similitude principle with ponderal doses of the medicinal substances,[4,5] using the infinitesimal doses in subsequent phase of his clinical practice, in view of the secondary action (homeostatic reaction) to be wakened with ponderal or infinitesimal doses:

"*In those older prescriptions of the often dangerous effects of medicines ingested in excessively large doses we notice certain states that were produced, not at the commencement, but toward the termination of these sad events, and which were of an exactly opposite nature to those that first appeared. These symptoms, the very reverse of the primary action or proper action of the medicines on the vital force are the reaction of the vital force of the organism, its secondary action, of which, however, there is seldom or hardly ever the least trace from experiments with moderate doses on healthy bodies, and from small doses none whatever. In the homeopathic curative operation the living organism reacts from these only so much as is requisite to raise the health again to the normal healthy state*" (*Organon*, paragraph 112).[3]

As my previous work has shown, the rebound effect (paradoxical reaction), observed after discontinuation of numerous modern palliative drugs, corresponds to the secondary action or vital reaction of the homeopathic model.[6–12]

Paradoxical or rebound symptom may be of greater intensity sometimes than the primarily suppressed symptom, expressing itself in variable period (hours to weeks) after the interruption or discontinuation of the medicine and of variable duration (hours to weeks), according to individual susceptibility (idiosyncrasy).

In this paper I review the scientific evidence that demonstrate rebound acid hypersecretion after the withdrawal of proton pump inhibitors, confirming Hahnemann's postulates.

Materials and methods

I searched the literature using the PubMed database and the keywords 'proton pump inhibitor' and 'rebound', selecting the most relevant papers and discussing the scientific evidence and its correspondence to homeopathic premises.

Results

Physiology of gastric acid secretion[13–15]

The secretion of gastric acid is stimulated by acetylcholine (vagus nerve), gastrin and histamine. The main functions of gastric acid are preventing bacterial overgrowth and enteric infections, digestion of proteins and absorption of iron, calcium, and vitamin B_{12}. But high levels of acid secretion affect the mucosal defense mechanisms causing acid-peptic disorders. To prevent such damage, gastric acid secretion is regulated by four pathways, showing a complex homeostatic autoregulation: (1) the parietal cells of the oxyntic mucosa (corpus and fundus of the stomach), which produce hydrochloric acid; (2) the enterochromaffin-like (ECL) cells of the oxyntic mucosa, which produces histamine, the main paracrine stimulant of acid secretion; (3) the G cells of the pyloric mucosa (antrum), which produces gastrin, the main hormonal stimulant of acid secretion; and (4) the D cells of oxyntic and pyloric mucosa, which produce somatostatin, the main paracrine inhibitor of acid secretion. Released from postganglionic neurons of the

autonomic nervous system, acetylcholine stimulates acid secretion by activating parietal cells; however, vagal stimulation has less influence than gastrin or histamine on gastric acid secretion.

Parietal cells contain abundant intracellular tubulovesicles that sequester H^+K^+-adenosine triphosphatase (H^+K^+-ATPase), known as the proton pump, which when stimulated fuse with apical membrane releasing hydrochloric acid. Proton pump inhibitors (PPIs) interrupt this process. Histamine is stored in secretory vesicles of ECL cells and is released by stimulation with gastrin, diffusing to neighboring parietal cells and stimulates acid secretion by binding to H_2 receptors on their surface. Gastrin is the principal mediator of meal-stimulated acid secretion and is critical to the growth of parietal and ECL cells of gastric mucosal. During the interdigestive phase, a feedback mechanism involving acid-induced somatostatin secretion attenuates acid secretion: somatostatin inhibits acid secretion by acting directly on parietal cells and indirectly by inhibiting histamine secretion from ECL cells and gastrin secretion from G cells. When acid concentration (secretion) is diminished (by antacids, antisecretory drugs, or atrophic gastritis), somatostatin secretion is inhibited, and gastrin secretion stimulated, resulting in rebound hypergastrinemia. This hypergastrinemia is the cause of rebound acid hypersecretion after discontinuation of PPIs.

Pathophysiology of rebound acid hypersecretion[16–18]

The US Food and Drugs Administration defines rebound acid hypersecretion as an increase in gastric acid secretion (basal and/or stimulated) above pretreatment levels following discontinuation of antisecretory therapy.[19] Rebound was initially reported in studies of the use of histamine H_2-receptor antagonists and was thought to be due to increased serum gastrin and/or up regulation of the H_2 receptors. Elevated gastrin levels or hypergastrinemia is a secondary effect that occurs during chronic inhibition of gastric acid secretion, such as with long-term antisecretory therapy. In man, gastrin is the primary regulator of gastric acid secretion, which is mediated by histamine released by the enterochromaffin-like (ECL) cell. Increased plasma gastrin stimulates and up regulates ECL cells to produce and release more histamine to stimulate the parietal cell. In addition, an increase in parietal cell mass may occur with the chronic use of antisecretory agents, and this may be an additional mechanism for increased acid secretion after discontinuation of therapy. Another possible cause of rebound acid secretion is increased sensitivity to histamine.

Rebound acid hypersecretion after antacids: Although not an antisecretory therapy, the neutralization of gastric acidity by antacids can also cause rebound after discontinuation of treatment. Rebound acid hypersecretion after antacids (aluminum/magnesium hydroxide and calcium carbonate) cited in previous reviews[20,21] was confirmed in others clinical trials,[22,23] reporting rebound phenomenon in healthy volunteers after 1 h of standard dose of antacids. Studies that evaluated the rebound acidity 2–3 h after suspension did not observe rebound.[24,25] As we shall see, the rebound effect of any drug is manifested at a specific time-point after cessation of treatment, usually related to half-life of drugs concerned and/or normalization of physiological changes. With antacids, it occurs within 1 h after a single dose.

Rebound acid hypersecretion after H_2-receptor antagonists: Similarly to other competitive antagonists that act on other physiological systems (beta-blockers in the heart, for example), the H_2-receptor antagonists cause rebound hyperfunction (acid hypersecretion) after withdrawal of the drug. Although the exact mechanism remains unclear, the main hypothesis is that it is due to increased responsiveness (up regulation) of the H_2-receptor to histamine stimulation after chronic, competitive inhibition, and impairment of the inhibitory arm of acid secretion (oxyntic mucosal inhibitory control).[26–29]

For any drug, time-point after drug withdrawal and appropriate primary or direct stimulus are of vital importance in the occurrence of rebound effects; studies that have not taken account of these aspects have not observed the phenomenon.[30–33] Taking these factors into account, Frislid *et al.*[34] demonstrated that there was a significant rebound acid hypersecretion to a meal 60–64 h after a 1-month course of ranitidine, despite the continuing presence of trace amounts of ranitidine at this time-point. This phenomenon was also observed studying nocturnal acid secretion 2–3 days after 4 weeks of either nizatidine, ranitidine or cimetidine.[35–38] Another study with ranitidine showed that acid hypersecretion occurred 60 h after cessation of treatment, returning to baseline after 10 days.[29] Studying asymptomatic healthy volunteers, Smith *et al.*[39] demonstrated in a placebo-controlled trial that the median duration of rebound dyspeptic symptoms was 2 days, with symptom severity being maximal on the second day after completion of the ranitidine tablets. However, as noted in the earlier studies at 3–11 days,[31–33] Kummer *et al.*[38] not observed significant alteration in maximal acid secretion 3 days after treatment. Thus, the rebound acid hypersecretion after H_2-receptor antagonists occurred within 2–3 days after 4 weeks of therapy, lasting 10 days.

Tolerance or tachyphylaxis to H_2-receptor antagonists: As for rebound acid hypersecretion, there is a well-established tolerance/tachyphylaxis phenomenon with the chronic use of H_2-receptor antagonists, manifesting in loss of efficacy in terms of acid secretion suppression.[40–45] As in the rebound effect, the magnitude of tolerance does not change with dose or treatment duration,[46,47] similar mechanisms explain both phenomena: enhanced responsiveness of the H_2-receptor to histamine, or impairment of the neurohormonal control of acid secretion, or hypergastrinemia are possible explanations for tolerance. The main clinical relevance is that H_2-receptor antagonist tolerance can cause peptic ulcer relapse,[48–51] and complications in the healing of esophagitis.[52,53]

Rebound acid hypersecretion after proton pump inhibitors: As previously mentioned, proton pump inhibitors (PPIs) block the final step in acid secretion, resulting in profound and persisting gastric hypoacidity and diminished antral D-cell release of somatostatin, with

concomitant increase G-cell release of gastrin and hypergastrinemia.[54,55] Rebound hypergastrinemia results in stimulation of ECL cells and hyperhistaminemia, which does not produce increase in gastric acid secretion since the proton pump is effectively blocked.[56] The stimulation of ECL cell proliferation induces an increase in the ECL cell mass, which persists longer than the effect of the PPI when the drug is discontinued. As in any rebound phenomenon, rebound acid hypersecretion is evident at a certain time-point after treatment, related to the half-life of the drug and the regeneration period of physiological changes. Studies that ignore these conditions did not demonstrate the rebound acid.[57] Rebound acid hypersecretion after a sufficient period of PPI treatment therefore occurs from the second week (PPIs half-life) until normalization of the ECL cell mass (about 2 months), i.e., 2–3 months after stopping treatment. The phenomenon is prolonged, lasting at least 2 months after a 2 months treatment course, with persisting significantly elevated submaximal and maximal acid hypersecretion.[58–64]

Paradoxically, although there is a tendency toward rebound in patients *Helicobacter pylori*-positive, rebound acid hypersecretion after PPI is more prolonged and pronounced in uninfected patients, despite *H. pylori*-positive developing more intense hypergastrinemia than *H. pylori*-negative during PPI therapy.[61,62,65] The difference between *H. pylori*-negative and -positive patients is most likely due to different pretreatment gastrin values moving the post-treatment gastrin values to parts of the concentration-response curve with a different slope with respect to the trophic effect on the ECL cells.[66] Moreover, in patients with *H. pylori*-induced gastritis not only in the antral but also in the oxyntic mucosa: atrophic gastritis will reduce the capacity to secrete acid (interleukin-1 is a very potent inhibitor of acid secretion) and therefore the magnitude and consequences of rebound acid hypersecretion. It should also be recalled that PPI treatment leads to increased oxyntic gastritis in *H. pylori*-positive individuals.[67–72]

In summary, the difference between *H. pylori*-negative and -positive groups with regard to rebound hypersecretion after PPI treatment may be due to oxyntic gastritis, which can mask any rebound phenomena in the infected subjects by enhanced elaboration of inflammatory mediators in the acid-secreting mucosa. However, eradication of *H. pylori* infections (antibiotic therapy) makes individuals more prone to development clinically significant rebound acid hypersecretion after PPI treatment.[73,74]

Tolerance to proton pump inhibitors: Similar to the H_2-receptor antagonists, rebound acid hypersecretion after PPI provides a theoretical basis for the possible development of tolerance to these drugs with chronic therapy, although there are few studies on the effects of long-term use.[75]

Other consequences of rebound hypergastrinemia[17,18,76]

Hypergastrinemia and neoplasia: Gastrin has trophic effects on many tissues and stimulates a number of tumor cell lines in culture, including colon cancer cells. Although there have been suggestions that hypergastrinemia is associated with an increase risk of colon cancer, two population-based case–control studies conducted in United Kingdom (1987–2002) and Denmark (1989–2005) found no evidence of such increase in patients using PPIs.[77,78]

There is reason to believe that patients with reflux disease will be more affected during the rebound acid hypersecretion period after a course of PPI treatment than before. The increase in gastroesophageal reflux disease seen during the last decades may be due to worsening of reflux symptoms caused by low-threshold PPI use to treat reflux symptoms. For the same reason, there is a possible effect of hypergastrinemia on the progression of Barrett's esophagus to cancer, in view of the marked rise in the incidence of adenocarcinoma at the cardioesophageal junction over the past two decades, as acid-suppressive therapy for gastroesophageal reflux disease has greatly increased.[79–81]

Experimental studies with animal models show that initial induction of hypergastrinemia causing acid hypersecretion was followed by acid hyposecretion and atrophy, with eventual development of gastric cancer.[82–84] A population-based cohort study in Denmark (1990–2003) showed increased incidence for gastric cancer among PPI users with the largest number of prescriptions or the longest follow-up compared with H_2-receptor antagonists users or non-users.[85] These observations suggested that hypergastrinemia may be a risk factor for development of gastric cancer, which one can suggest might also be relevant to the proton pump inhibitor situation.

Hypergastrinemia and carcinoid tumours: Carcinoid tumours have long been recognized as a consequence of the hypergastrinemia of the Zollinger–Ellison syndrome and atrophic gastritis. Rats exposed to long-term high doses of omeprazole developed enterochromaffin-like cell hyperplasia and gastric carcinoids.[86] It was probable that proton pump inhibitor inducing hypergastrinemia was leading to the enterochromaffin-like cell hyperplasia and carcinoid tumours, since similar results could be obtained with long-term administration of gastrin.[87] However, there are no studies that show similar results in humans.

Similarly, the increased incidence of gastric carcinoid tumours in last three decades (400% in men and 900% in women) coincides with the widespread marketing of PPIs.[88–90] According to McCarthy,[76] the scientific basis for expecting long-term PPI use to cause carcinoid tumours is quite strong and merits serious attention. Hypergastrinemia may also stimulate carcinoid development or growth in other sites.

Clinical evidence of rebound acid hypersecretion after PPI withdrawal

Extending a previous study[61] to estimate the duration of hypersecretion and to elucidate the role of ECL cell in rebound acid hypersecretion, Fossmark *et al.*[64] studied patients waiting for anti-reflux surgery who discontinued the use a PPI daily >1 year, measuring gastrin, serum chromogranin-A (CgA) and pentagastrin stimulated acid output before and at 4, 8, 16 and 26 weeks postoperatively.

Oxyntic mucosal biopsies were collected before and 26 weeks after operation for counting of histidine decarboxylase (HDC) immunoreactive cells. Pentagastrin stimulated acid secretion was higher at 4 and 8 weeks than at 26 weeks after surgery while gastrin and CgA were significantly reduced at 4 and 8 weeks. The number of HDC immunoreactive cells was reduced by 60% at 26 weeks postoperative. These results suggest that rebound acid hypersecretion lasts more than 8 weeks, but less than 26 weeks after long-term PPI, and that not only the parietal cell mass, but also ECL cell mass and activity are involved.

To evaluate the occurrence and the clinical relevance of rebound acid hypersecretion after discontinuation of PPIs, Hunfeld *et al.*[91] performed a systematic review including eight studies (sample size 6–32). Five studies (including four randomized studies) did not find any evidence for rebound acid hypersecretion after PPI withdrawal. Of the remaining three uncontrolled trials, two studies suggested that rebound acid hypersecretion may occur in *H. pylori*-negative patients after 8 weeks of PPIs. The authors concluded that there is no strong evidence for a clinically relevant increased acid production after withdrawal of PPI therapy. Criticizing the studies included in this systematic review, which did not have, as an inclusion criterion sufficient duration of PPI therapy to develop significant ECL cell hyperplasia and subsequent acid rebound, Fossmark and Waldum[92] reiterated that it is impossible to evaluate rebound acid hypersecretion after a single dose of PPI, nor after 25 days use, although the studies had a randomized design: "*these five studies merely show that PPI must be used more than 1–25 days to induce rebound acid hypersecretion*".

In a double-blind, placebo-controlled trial, 120 healthy volunteers were randomized to 12 weeks of placebo or 8 weeks of esomeprazole 40 mg/day followed by 4 weeks with placebo. The Gastrointestinal Symptom Rating Scale (GSRS) was filled out weekly, and a score of >2 on 1 of the questions regarding heartburn, acid regurgitation, or dyspepsia was defined as a clinically relevant acid-related symptoms. As indirect measures of gastric acid secretion and ECL cell mass, plasma levels of gastrin (P-gastrin) and serum levels of chromogranin-A (P-CgA) were measured at weeks 0, 4, 8 and 12. There were no significant differences between groups in GSRS scores during weeks 0–9. GSRS scores for acid-related symptoms were significantly higher in the PPI group at week 10 (1.4 ± 1.4 *vs.* 1.2 ± 0.9; $P = 0.023$), week 11 (1.4 ± 1.4 *vs.* 1.2 ± 0.9; $P = 0.009$), and week 12 (1.3 ± 1.2 *vs.* 1.0 ± 0.3; $P = 0.001$). Forty-four percent (26/59) of verum group reported ≥ 1 relevant, acid-related symptoms in weeks 9–12 compared with 15% (9/59; $P < 0.001$) in the placebo group. The proportion reporting dyspepsia, heartburn, or acid regurgitation in the PPI group was 22% (13/59) at week 10, 22% (13/59) at week 11, and 21% (12/58) at week 12. Corresponding figures in the placebo group were 7% at week 10 ($P = 0.034$), 5% at week 11 ($P = 0.013$), and 2% at week 12 ($P = 0.001$). In the PPI group, P-gastrin was significantly correlated with the GSRS score at week 8 and 12. Compared to placebo group, P-CgA was significantly higher and above the normal range in the PPI group at weeks 8 and 12, reflecting proliferative changes of the ECL cells and sustained increased acid secretory capacity. Authors conclude that PPI therapy for 8 weeks induces rebound acid hypersecretion in a significant proportion of asymptomatic subjects after withdrawal, and this phenomenon is equally relevant in patients treated long term with PPIs.[93]

In similar study, 48 healthy *H. pylori*-negative volunteers were randomized in a double-blinded manner to treatment with either pantoprazole (40 mg/day) or placebo for 28 days. Dyspeptic symptoms were registered daily using the Glasgow Dyspepsia Score (GDS) 2 weeks before, during, and 6 weeks after treatment. Plasma levels of gastrin and serum levels of CgA were measured before, during, and after treatment. No significant differences between the symptom severity scores of the two groups were shown during the treatment period. During the first week after discontinuation of treatment, the pantoprazole group had a mean symptom score of 5.7 ± 11.7 *vs.* 0.74 ± 2.6 in the placebo group ($P < 0.01$). In the verum group, a total of 11 out of 25 (44%) individuals developed dyspepsia compared with 2 out 23 (9%) in the placebo group. During the second week, the verum group had a mean symptom score of 1.6 ± 3.4 *vs.* 0.0 ± 0.0 in the placebo group ($P < 0.05$); a total of 6 out 25 (24%) participants developed dyspepsia in verum group compared with none in the placebo group ($P = 0.003$). During the remaining 4 weeks, the symptom score did not significantly differ between the groups. In the verum group, the median duration of rebound symptoms was 4 days, and the onset of symptoms was most commonly observed at days 5 and 6 after cessation of therapy. During the first week after treatment withdrawal, symptom scores correlated with basal ($P < 0.01$) and meal-stimulated ($P < 0.01$) gastrin levels at the end of treatment suggesting that these symptoms are due to acid rebound hypersecretion and seem to be related to the degree of acid inhibition. Authors concluded that a 4-week course of pantoprazole seems to induce acid rebound hypersecretion in previously asymptomatic healthy *H. pylori*-negative individuals.[94]

Indirectly assessing whether the rebound acid hypersecretion also occurs in symptomatically treated patients, studies described the recurrence of symptoms in approximately 70% of long-term PPI users after discontinuation of therapy.[95,96]

Discussion

As with other classes of drugs (anti-inflammatories, bronchodilators, antidepressants, and statins),[8–12] in this study I have reviewed evidence for the relationship between proton pump inhibitors withdrawal and rebound acid hypersecretion, and worsening of dyspeptic diseases.

Proton pump inhibitors are among the most frequently used medicines worldwide and are an important cost for health-care system in many countries, being prescribed for a wide variety of upper gastrointestinal symptoms on the basis that they might be acid induced and therefore may benefit from such treatment.[97–101] For instance, the total use of PPIs increased 7-fold from 1993 to 2007 in

Denmark, with the use increased substantially from 20 to 33 defined daily doses per 1000 individuals per day from 2003 to 2007. In 2006, approximately 7% of the Danish population was treated with a PPI. While use of H_2-receptor antagonists declined 72% from 1995 to 2006 in Australia, the use of PPIs increased by 1318%.[102–105]

Although this liberal employment of PPIs is recommended by many dyspepsia guidelines,[106–108] it is well documented that these drugs are often inappropriately prescribed for minor symptoms and without clear indications, where the effects of acid-suppressive therapy is controversial.[100,104,109–113] As a result, a large proportion of patients now prescribed PPIs do not have acid-related symptoms and therefore have no true indications for such therapy. Studies also have shown that up to 33% of patients who initiate PPI treatment redeem repeat prescriptions without an obvious indication for maintenance therapy.[100,114] This may complicate discontinuation of PPIs because of the development of rebound acid hypersecretion, leading to recurrence of symptoms of underlying acid-related disease (heartburn, acid regurgitation and dyspepsia) that might result in resumption of therapy.[95,96]

McColl and Gillen[115] say that "*these drugs induce symptoms means that such liberal prescribing is likely to be creating the disease the drugs are designed to treat and causing patients with no previous need for such therapy to require intermittent or long-term treatment*". They propose a series of changes in prescribing habits of PPIs, among them efforts to try to restrict PPI use to disorders likely to derive benefit, and obliged information to patients about rebound acid hypersecretion and its potential effects.

This authors' warning, signaling that improper use of PPIs may cause similar diseases to those which are designed to treat, echoes Hahnemann's alerts about the harmful effects of enantiophatic or palliative treatment, and indirectly corroborating the principle of 'like cures like'. Creating or exacerbating dyspeptic diseases, as well as leading to cancer, the indiscriminate use of PPIs may cause "*another more serious disease or, frequently, incurability, even danger to life and death itself*": "*If these ill-effects are produced, as may very naturally be expected from the antipathic employment of medicines, the ordinary physician imagines he can get over the difficulty by giving, at each renewed aggravation, a stronger dose of the remedy, whereby an equally transient suppression is effected; and as there then is a still greater necessity for giving everincreasing quantities of the palliative there ensues either another more serious disease or, frequently, incurability, even danger to life and death itself, but never a cure of a disease of considerable or of long standing*" (*Organon*, paragraph 60).[3]

There is evidence that the acid rebound occurs within 1 h after antacids, 2 days after 4 weeks of H_2-receptor antagonists, and 1 or 2 weeks after 4 or 8 weeks of PPIs. The rebound phenomenon lasts for 10 days after 4 weeks of H_2-receptor antagonists, and 2 or 4 weeks after 4 or 8 weeks of PPIs. Around 40% of users of PPI reported rebound acid hypersecretion. The *American Hospital Formulary Service* described recurrence of peptic ulcers in 41% of patients after 1–4 weeks of discontinuing chronic therapy with cimetidine. Perforation of chronic peptic ulcers were also reported.[6,7,116]

PPIs therapy results in delayed (2–3 months after withdrawal) rebound due to increase in the ECL cell mass and the corresponding longer period for physiological normalization. In such cases, the rebound acid hypersecretion may also be more prolonged (2 months), causing major consequences.

Confirming the principle of similarity as 'natural law', the continuing reports of increased iatrogenic events after withdrawal of palliative modern drugs demonstrates the importance of the rebound phenomenon (homeopathic vital reaction) in promoting deep alterations in the homeostatic balance. Using this rebound effect of curative form, homeopathy stimulates the body to react against their own diseases.

Conclusion

The secondary action or vital reaction of the homeopathic model is based on studies of the rebound effect or paradoxical reaction of hundreds of modern medicines, utilized according to the 'contrary' principle (*contraria contrariis*). The development of tolerance to a repeatedly administered drug is a result of the same adaptive process.

Rebound effects may be idiosyncratic, manifesting only in a small proportion of the individuals. But these paradoxical events assume epidemiological importance when we consider the enormous current consumption of such drugs.[9–12] In the case of PPIs, the rebound effect assumes greater importance because they widely used and rebound occurs in a large percentage of users (around 40%).

Analogously to traditional homeopathic medicines, the rebound effect of modern drugs can be used for therapeutic purposes, namely to stimulate homeostatic healing reactions provided they are prescribed according to the principle of similitude of symptoms as it was described in previous studies.[6,7,117,118]

Following Hahnemann's reasoning in this proposal, we are incorporating 1250 new conventional drugs into *Homeopathic Materia Medica*, broadening the spectrum of action of homeopathic therapy and the scientific basis of 'like cures like' principle.[119]

We will soon make available online the project 'New Homeopathic Medicines: use of modern drugs according to the principle of similitude', divided into three modules: (1) *Scientific Basis of the Principle of Similitude in Modern Pharmacology*; (2) *Homeopathic Materia Medica of Modern Drugs*; and (3) *Homeopathic Repertory of Modern Drugs*.[120] We invite the collaboration of the homeopathic community in this project.

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