INTERACTIONS BETWEEN MEDICINAL GASES AND OTHER MEDICINAL PRODUCTS: DEVELOPMENT OF A HOSPITAL DRUG DATABASE

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Introduction

The Deliberation n.°56/CD/2008 from the Portuguese Authority of Medicines and Health Products (INFARMED) approves the regulation of medicinal gases laid out by the Decree-Law n.°176/2006, which considers them as medicines for human use. This Deliberation addresses the manufacture, packaging, labeling, package leaflet, technical management, transportation, distribution, marketing, supply and home delivery of medicinal gases(1). Although most medicinal gases have been used in health care services for a long time, they have only recently been regulated as drugs. As a result of this new legislation, pharmacists took most of the responsibilities associated with this new pharmacotherapeutic group. In this context, pharmacists play a proactive role by providing essential information for the proper use of these medicines.

Objectives

The aim of this study is to develop a database of medicinal gases that allows hospital pharmacists to detect medicinal gases/other medicinal products interactions and validate medical prescriptions in a quick, safe and effective way.

Methods

Review of the summary of product characteristics (SPC) of all medicinal gases currently available in Portugal and consultation with the manufacturers of medicinal gases and analysis of responses. A literature review was also performed, through research and analysis of articles obtained from PubMed since January/2007 to September/2012, intersecting the terms “medicinal gases” and “medical gases”.

Results

A total of 6 medicinal gases currently available in Portugal were analyzed: medicinal air, nitric oxide, nitrous oxide, nitrous oxide/oxygen, oxygen and xenon. The main interactions of these gases with other medicinal products are described below:

Medicinal Gases	Drug interactions
Medicinal air	- No interactions were found with medicinal air.
Oxygen	- **Antiarrhythmics (e.g. amiodarone)** - Synergistic effect: formation of reactive oxygen species (ROS), leading to an increase of pulmonary damage, interstitial pneumonitis, fibrosis and acute respiratory distress syndrome (ARDS)(2). Phospholipidosis can contribute to these injuries(3). - **Bleomycin** - Synergistic effect: production of ROS in alveolar interstitial tissue due to the enzyme deficiency of bleomycin hydrolase in lung tissue which results in acute fibrosis(4). - **Chloroquine** - By increasing oxygen concentration the half maximal inhibitory concentration (IC_{50}) decreases significantly, in other words, efficacy/toxicity of chloroquine is augmented as the dose of oxygen increases(5). - **Phenothiazines (e.g. chlorpromazine)** - These drugs stimulate the loss of effective hemoglobin concentration and consequently cause tissue hypoxia(6). A dose-dependent reduction in seizure threshold can also be triggered, chlorpromazine and clozapine carry a higher risk than other antipsychotics(7). - **Corticosteroids** - Modulation of immune response and improved mechanisms of tissue repair may lead to an eventual reduction in the dose of corticosteroids(8), (9). - **Doxorubicin** - Induction of oxidative stress due to the production of ROS that result from its metabolism and that will contribute to tissue injury. The ROS play an essential role in the pathogenesis of doxorubicin-induced cardiotoxicity(10). - **Nitrofurantoin** - Lung lesions can occur due to lymphocytosis in the alveoli (non-cytotoxic pneumonitis) or by increasing the production of ROS in lung cells(11),(3). - **Phytonadione** - Vitamin K1 is slowly degraded by atmospheric oxygen(12). - **Sympathomimetics** - Intensification of consumption and metabolism of oxygen as a result of central stimulation. Vasoconstriction synergy was also found(9).
Nitrous Oxide (N_2O)	- **Cyanocobalamin** - N_2O irreversibly oxidizes the cobalt moiety of vitamin B12, consequently inactivating the cobalamin-dependent enzyme, methionine synthase(13). - **Drugs that depress the Central Nervous System (CNS)** - Additive effect: N_2O, a NMDA antagonist, may increase the release of beta-endorphins and naturally occurring opioid-like substances. It can directly bind to mu, delta and kappa opiate receptors(14). - **Methotrexate** - Methotrexate inhibits dihyrofolate reductase and blocks regeneration of tetrahydrofolate from dihydrofolate. Through depletion of 5-methyl-THF, methothrexate diminishes methionine synthase activity, enhancing the effect of N_2O(14).

Medicinal Gases	Drug interactions
Nitric Oxide (NO)	- **Oxygen** - Associated with high concentrations of oxygen, gaseous NO slowly forms a toxic product - nitrogen dioxide (NO_2). Additionally, NO may react with reactive oxygen species such as superoxide to form reactive nitrogen species (RNS) such as peroxynitrite ($ONOO^-$)(15),(16). - **Nitric oxide donor drugs (nitroglycerin, nitroprusside sodium)** - They promote stabilization of the NO radical until its release and enhancement of pulmonary hypertension treatment(17). - **Vasoconstrictors (phenylephrine, almitrine)** - May further enhance the activity of NO in treating acute respiratory failure, allowing a larger fraction of pulmonary blood flow to be redirected to ventilated areas(18). - **Phosphodiesterase Inhibitors** - Synergistic and additive effects have been reported and combination therapy may be an option in refractory cases(19). - **Prostacyclin** - Combination therapy may have additive effects for the treatment of pulmonary hypertension. When aerosolized, its vasodilatory action in ventilated areas should be similar to NO without promoting systemic hypotension(20). - **Prilocaine, Sulfonamides, Amyl nitrate** - Caution should be used with long-term use as it has been associated with the onset of methemoglobinemia(21),(22).
Xenon	- **Beta-blockers** - Compensatory cardiovascular reactions may be affected by beta-blockers during anesthesia, however these effects can be minimized by administering beta sympathomimetics during surgery. Beta-blockers should be continued through the perioperative period in patients already taking them(23). - **Drugs that depress the CNS** - NMDA receptor antagonists, such as xenon, suppress central sensitization, prevent the development of opioid tolerance and reduce postoperative pain(24). - **Other inhaled anesthetic agents and MAOIs (Monoamine oxidase inhibitors)** - Should be considered for discontinuation at least 2 weeks prior to surgery due to the potential for severe intraoperative drug interactions: hypertension, hypotension, hyperpyrexia, hyperreflexia and convulsions(23),(25). - **Dihydropyridine calcium channel blockers** - Inhalation of xenon may cause clear hypotension when taken concomitantly(25). - **Indirect-sympathomimetics (e.g. amphetamine, psychostimulants, ephedrine)** - Risk of perioperative hypertension, to meet scheduled surgery treatment should be discontinued for several days before surgery(25).

Discussion/Conclusions

The prescription of medicinal gases by healthcare professionals requires the same pharmacotherapeutic monitoring commitment and pharmacovigilance as other drugs, in order to promote rational use of medicines and patient welfare.
There is a panoply of drugs that interact with medicinal gases and a number of mechanisms that explain these interactions which can be beneficial or pejorative. There are also essential and appropriate measures to be taken to prevent major side effects. The produced database is a valuable tool for Portuguese hospital pharmacists that dispense medicinal gases, contributing to validate prescriptions of these medicines quickly and effectively.

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Conflicts of Interest: Nothing to disclose.

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