of similar structural and pharmacologic characteristics, such as fenfluramine and dexfenfluramine (brand names Ponderal®, Isomeride®; Servier, Redux®; Wyeth) have been withdrawn from the world market since 1997. Indeed, these compounds, derived from the amphetamines, are known to be responsible for pulmonary arterial hypertension (PAH) and valvular heart disease (VHD). Subsequent studies published in 2000 have shown the determinant role of their common active metabolite, norfenfluramine, which is present at equal plasma concentrations after fenfluramine, dexfenfluramine, or benfluorex intake at recommended dosages. Norfenfluramine induces VHD and PAH by stimulation of a serotonin receptor subtype, expressed on both aortic and mitral valve leaflets as well as in pulmonary arteries.

Despite several case reports stressing the association of PAH and/or VHD with benfluorex exposure, benfluorex remained available in France until November 2009. Our initial case-control study published in 2010 put forward the toxicity and the VHD risk of benfluorex, thus leading to the withdrawal of benfluorex from the European and world market, respectively. This pilot study opened the avenue to further pharmacoepidemiologic studies validating our results and giving detailed data on the benfluorex risks in larger populations.

Actual human consequences of longer than 33 years of marketing authorization of benfluorex on patients only in France are estimated at ~1300 to 1800 deaths and 3100 to 4200 VHD-related hospitalizations. To date, there is no estimation of worldwide mortality due to benfluorex use.

Disclosure of Interest: None declared.

Reference

Frachon I, Etienne Y, Jobic Y, et al. Benfluorex and unexplained valvular heart disease: a case-control study. *PLoS ONE*. 2010;5:e10128.

TREATING RARE INBORN ERRORS OF METABOLISM: FROM THEORY TO PRACTICE

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Summary: Recent public discussion on new treatment options in orphan diseases has focused on the great promise they hold, as well as the high cost they generate for our health systems. Instead, this presentation will consider new facts and difficulties arising from these treatments from a purely medical standpoint and discuss some of them using examples from our daily practice.

Enzyme-replacement therapy (ERT) for certain lysosomal storage disorders (LSD) does not cross the blood-brain barrier (BBB) and does not, therefore, influence disease progression in the brain. How should we take into account the extent and speed of progress of lysosomal brain disease? Even at the peripheral level, definition of satisfactory treatment, efficacy is not straightforward. Miglustat, an example for substrate reduction therapy, has the advantage to cross the BBB. Recently, it has been used in several neuronopathic LSD, including early-manifesting Gaucher type III disease. What is the impact of inhibiting the synthesis of complex molecules in a brain that is still under construction? What benefice can be expected and at what age?

Sapropterin (Kuvan®) is a pharmacologic chaperone that has recently been introduced for the treatment of phenylketonuria. There is, however, a wide interindividual variation of response to this drug; it can in only rare instances completely replace the equally or more effective dietary treatment. Treatment policies vary among countries and even within countries.

Disclosure of Interest: M. Gautschi: grant/research support from Shire, Milupa, and Orphan Europe.

TRANSIENT RECEPTOR POTENTIAL CHANNELS AS NOVEL DRUG TARGETS

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Summary: At least 6 members of the family of the transient receptor potential (TRP) channels are expressed in defined subpopulations of primary sensory neurons (nociceptors), where they mediate acute nociceptive responses and contribute to allodynic and hyperalgesic conditions. Most prominent channels are the vanilloid 1 (TRPV1), which is activated by capsaicin, protons, and certain eicosanoids, and the ankyrin 1 (TRPA1). TRPA1 is uniquely gated by an unprecedented series of reactive exogenous (mustard oil, cinnamaldehyde and others) and endogenous molecules. These latter molecules include byproducts of oxidative stress, as hydrogen peroxide, 4-hydroxynonenal, oxononenal, and many others electrophilic agonists, which, by binding to key cysteine residues, cause channel activation and nociceptor stimulation. All TRPA1-expressing neurons and the majority of TRPV1-expressing neurons express and release sensory neuropeptides, which mediate neurogenic inflammatory responses. Calcitonin gene–related peptide (CGRP) released from perivascular trigeminal nerve endings upon TRPV1 or TRPA1 stimulation has been now recognized as a major contributing factor of migraine headaches. A series of agents, known to trigger migraine attacks, have been identified as selective stimulants of TRPV1 or TRPA1, thereby producing CGRP-dependent meningeal vasodilatation. There is growing evidence that TRPV1 and, even at a larger extent, TRPA1 contribute to thermal and mechanical hypersensitivity in models of inflammatory and neuropathic pain. In particular, recent findings underscore the critical role of TRPA1 in models of chemotherapeutic-induced peripheral neuropathy. The desensitizing action on nociceptor function of topical and repeated application of the TRPV1 agonist, capsaicin, has been used for a long time for the treatment of pain in postherpetic neuralgia and in diabetic neuropathy. In contrast, clinical development of TRPV1 antagonists has been hampered by unexpected evidence obtained in Phase I studies of their ability to increase body temperature and heat pain threshold. The underlying hypothesis that TRPA1 plays a major role in pain associated with increases in oxidative stress is boosting major efforts in the discovery and development of TRPA1 antagonists.

Disclosure of Interest: P. Geppetti: shareholder of Pharmeste Srl; grant/research support from Chiesi Pharm, AstraZeneca, and Ibsen; consultant for Sanofi and Grunenthal.

TARGETED THERAPIES IN HEMATOLOGICAL MALIGNANCIES

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Summary: Knowledge of the driving molecular abnormalities that underlie the malignant phenotype has afforded opportunity to pharmacologically, and with surgical precision, target cancers. Historically, therapy for hematologic malignancies has been associated with toxicity to normal bone marrow and lymphoid progenitors. This results in myelosuppression and immunosuppression. The discovery of the Philadelphia chromosome t (9:22) and subsequent clarification that t (9:22)(q34:q11) resulted in the expression of the chimeric growth–promoting protein BCR-ABL led to the development