Variability in Human Drug Response
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Management of variability through dosage form design

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ABSTRACT

The repercussions of the formulation upon the variability of the pharmacological response are not uniform, so it is difficult to draw general conclusions. The variability of the response is greatly dependent upon the parameter assessed, the disease itself, the age and state of the patient, the drug and its dosage. The type of formulation, i.e. MRF bid or od, but not the brand influence the variability of the response. For drugs like theophylline, 5-aminosalicylic acid and budenoside a MRF reduces the variability of the response. On the other hand, for antihypertensive and antianginal drugs, such as verapamil, diltiazem, propranolol, and prazosin a MRF does not affect or decreases the variability of the response; however, nifedipine MRF increases the variability of parameters such as diastolic blood pressure, heart rate, time to elicit chest pain and total time of exercise. In addition, the formulation does not modify the variability of the response to opioid analgesics, NSAIDs, L-dopa, and diuretics (at steady state). Finally, a MRF increases the variability of undesired effects of benzodiazepines and of desired effects of procainamide and glipizide.

Key words: modified release formulations, pharmacodynamics, undesired effects, coefficient of variation, human.

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INTRODUCTION

Modified release oral formulations (MRF) are used not only to prolong the effect of a drug when it is rapidly eliminated, but also to modulate the pharmacological response of a drug. These goals are attained by changing the kinetics of absorption of the drug, by controlling the site of absorption, and by maintaining a steady effect. This review aims to evaluate the influence of a MRF on the variability of the response, desired and undesired, according to each of the objectives of a MRF. To minimize differences not due to the formulation, most

of the literature discussed in this review includes articles where both the immediate release formulation (IRF) and the MRF were studied and compared in the same patients. All along the manuscript, variability will be assessed as the coefficient of variation (CV), calculated by dividing the standard deviation by the mean, and expressed as a percentage. We have assumed that a formulation-induced 30% or more difference in CV may have clinical repercussions, and this value has been used as threshold to accept a change in variability of the response. The difference in CV has been estimated with the following equation $(CV_{IRF} - CV_{MRF})/CV_{IRF}$.

MRF AIMED TO PROLONG THE DURATION OF THE EFFECT

In patients with uncomplicated asthma, average CV of the peak expiratory flow rate (PEFR) as a function of time following the intake of theophylline IRF is 85 ± 23% (± SD). The variability of the response to theophylline IRF is apparently not influenced by the severity of the disease, i.e. in patients with chronic obstructive lung disease (COLD), mean CV is 82 ± 48% [1]. When the CV of the PEFR is plotted as a function of time, it is apparent that the CV varies greatly soon after drug administration, variability that decreases to reach a minimum around 6 h, and increases later on (Figure 1).

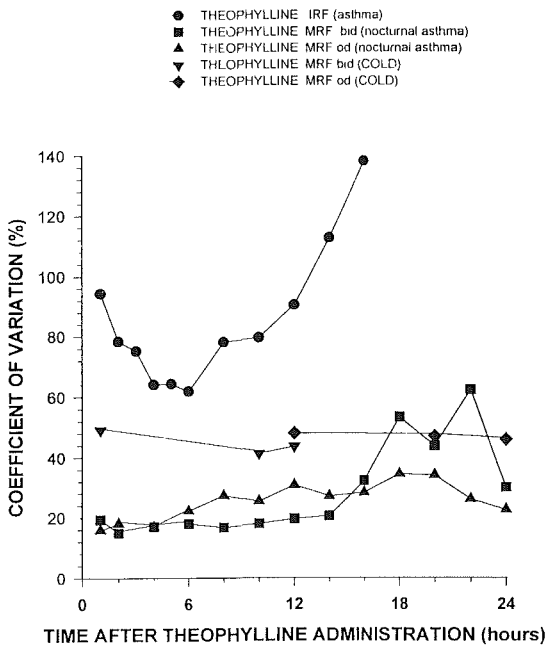

Figure 1. Coefficient of variation of the peak expiratory flow rate as a function of time of patients with uncomplicated asthma receiving theophylline IRF, in patients with nocturnal asthma taking theophylline MRF twice daily (bid) or once daily (od), and in patients with chronic obstructive lung disease (COLD) treated with theophylline MRF bid or od.

The use of a MRF of theophylline is justified because of the need to administer theophylline IRF four times a day and more importantly, to control nocturnal asthma. Originally, formulations allowed a twice-daily (MRF bid) administration of theophylline, and more recently once-daily formulations (MRF od) have been marketed. A double blind cross-over study, including patients with nocturnal asthma, compared the effect of theophylline MRF bid given at 8:00 and 20:00 h with theophylline MRF od given 20:00 h [2]; average CVs of PEFR are low for both formulations, i.e. 28 ± 16 and 25 ± 6%, respectively. Following the administration of theophylline MRF bid, the CV of the PEFR remains rather stable all along the day, however it increases during the night to reach at 2:00 a.m. values more than twice those observed during the day (Figure 1). On the other hand, the CV estimated with MRF od remains remarkably stable all along the day. In patients with reversible COLD, when Theo-Dur® MRF bid is compared with Uniphyl® MRF od, the average CVs of PEFR are of 45 ± 4 and 47 ± 1%, respectively, values that remain stable all along the day [3].

The CV of the PEFR assessed in patients given theophylline IRF is negatively associated with theophylline plasma concentrations (r = 0.793) (Figure 2). In fact, the CV of the PEFR

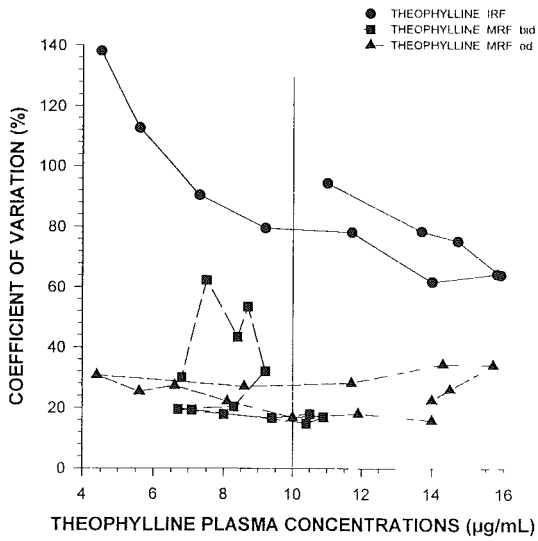

Figure 2. Coefficient of variation of the peak expiratory flow rate as a function of theophylline plasma concentrations in patients with uncomplicated asthma receiving theophylline IRF, and in patients with chronic obstructive lung disease (COLD) treated with theophylline MRF twice daily (bid) or once daily (od).

is rather stable above the theoretical minimal effective plasma concentration of 10 µg/mL, but increases below this threshold. In contrast, with theophylline MRF bid, the CV of PEFR shows an increase unrelated to the changes in theophylline plasma concentration. On the other hand,

the CV of the PEFR in response to theophylline MRF od is independent of theophylline plasma concentrations [3].Despite differences in the design of the studies considered [1-3], the analysis of these reports suggests that by comparison to theophylline IRF, the use of a MRF reduces the CV of the pharmacological response of theophylline, the magnitude of the reduction being associated to the disease rather than the type of MRF (bid or od) or the brand.

In a double-blind, double-dummy, crossover study, patients received either 8 mg of salbutamol MRF bid or 4 mg in an IRF every 6 hours (q6h) for 2 weeks, and the effect of salbutamol was evaluated by documenting serial PEFR over a 12 h period. At steady state, average CVs of PEFR are 18 ± 3 and 17 ± 1% for the MRF and IRF, respectively. The variability in the response is not affected by the fluctuations in salbutamol plasma concentrations [4]. Moreover, the brand does not appear to influence the CV of PEFR, i.e. 21.1% v.s. 24.0% for Ethypharm Salbutamol SR® and Volmax®, respectively.

Opioid analgesics are frequently given in MRFs, since they are used over long periods in patients with cancer or other chronic pathologies. The CV of the analgesic response varies with the specific response taken into consideration, the intensity of pain, the dose used, and the cause of pain. In patients with stable cancer, the CV of the overall ordinal pain intensity score of morphine injected s.c. is around 50% [5], CV that increases by around 30% when the drug is administered by oral or rectal routes. With reference to the oral solution, the use of a MRF for oral or rectal routes do not change the CV [5-7]. The time of the day at which the response to morphine is evaluated does not influence the CV of the response [6].

The brand of morphine MRF does not influence the CV of the response. For instance, the CV of the response to MS Contin® MRF bid given to patients with stable cancer varies from 71 to 87%, compared to 70% for the solution of morphine [7-9]. The CV of the peak pain relief of Oramorph SR® MRF bid administered to patients undergoing an abdominal intervention is 54%, compared with 49% for MS Contin® MRF [10]. The CV is slightly higher when the response is evaluated in patients with advanced cancer, i.e. around 68% [6]. The CVs of the global pain index score (pain intensity score times the number of hours spent each day at that level of pain) assessed in patients with stable cancer are 21, 22 and 27% following the administration of the solution of morphine, MS Contin® MRF tablets, and M-Eslon® MRF capsules, respectively [11].

The CVs of the analgesic response to various opioid derivatives are similar. The CV of the antialgic response to oxycodone given in a solution q4h assessed by the mean pain relief with a visual analogue scale (VAS) is 88% [12]. In patients with stable cancer-related pain, when oxycodone MRF is compared to MS Contin® MRF the CV of the mean daily pain intensity is 63% vs 47%, respectively [13]. In patients with stable cancer pain given oxycodone MRF or hydromorphone MRF, the CVs of the categorical pain intensity are 40 v.s. 37%, respectively [14]. These examples show that the MRF of an opioid derivative given to patients with cancer, does not modify the variability of the analgesic response.

Concerning the variability of undesirable effects, such as nausea, it was shown in patients with advanced cancer-related pain, that the CVs of the VAS score of nausea induced by a solution of morphine or by MS Contin MRF given at doses ranging from 40 to 400 mg are 31 and 22%, respectively [15]. It is unclear whether the dose of morphine or the severity of the pain increase the CV of the VAS scores for nausea, i.e. in patients with chronic severe cancer-related pain receiving doses of 60 to 800 mg of morphine solution or MRF, the CVs are 230 and 280%, respectively [16]. On the other hand, in patients with stable cancer pain receiving 24 to 480 mg of morphine, the CV for the VAS score of nausea is 107% compared

to 120% when the patients received 60 to 1200 mg of morphine MRF [6]. Similar variability is seen in patients with stable cancer pain receiving oxycodone or hydromorphone MRF, i.e. the CV for the VAS score of nausea is 104% [14].

With procainamide IRF, at average therapeutical plasma concentrations of 9.1 ± 3.4 μg/mL (± SD) abolishing about 40% of premature ventricular depolarizations (PVD) complexes, the CV of the decrease in PVD is 53% (Figure 3), value close to the CV of the incidence of PVD in absence of drug. At toxic plasma concentrations of procainamide of 22.8 8.5 μg/mL, when PVD are reduced by 97%, the CV increases to 105% [17]. Procainamide MRF given q6h (Procan SR®) or bid (Procanbid®) at a dose unable to reduce the PVD (1000 mg/day) does not change the CV of the incidence of PVD (Figure 3). However, at doses of 2000 and 4000 mg/day, able to reduce the incidence of PVD by 42 and 60% respectively, the CVs of the response increase to values ranging from 136 to 246% (Figure 3), and that despite rather stable procainamide plasma concentrations [18]. These results suggest that high doses of procainamide aimed to reduce maximally the incidence of PVD increase the CV of its response. Furthermore, a MRF increases the CV of the response possibly because it generates lower plasma concentrations of procainamide than the IRF.

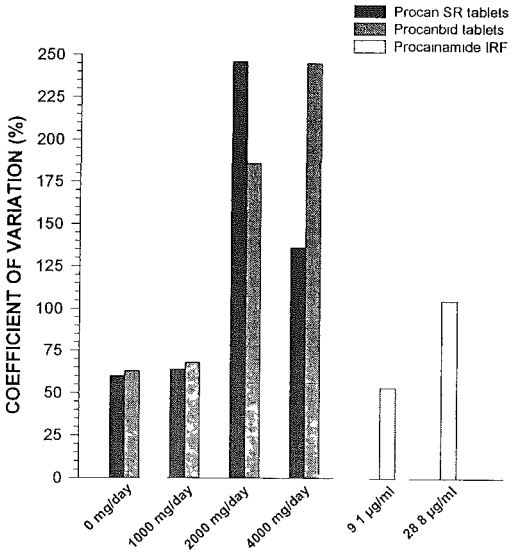

Figure 3. Influence of the daily dose of two MRFs of procainamide (Procan SR given q6h and Procanbid given twice daily) and of therapeutic and toxic plasma concentrations of procainamide given with an IRF on the coefficient of variation of the effect of procainamide on ventricular premature depolarization.

MRF AIMED TO IMPROVE THE SITE OF DRUG DELIVERY

In recent years, 5-aminosalicylic acid has been used as an enema whenever ulcerative colitis lesions are distal, and oral formulations are used for the disease localized proximally to the splenic flexure. The response to 1.5 g of rectal 5-aminosalicylic acid is rather variable, i.e. the CV of the activity index is 103% [19]. At low oral doses of 5-aminosalicylic acid given as a MRF (1 g/day) the CV of the activity index is similar to that observed with placebo, i.e. 71% v.s. 66. Increases in the oral dose of 5-aminosalicylic acid MRF enhance efficacy without major repercussions on the CV of the response, i.e. 78 and 83% for 2 and 4 g/day doses, respectively [20]. The CV of the response to low doses of oral 5-aminosalicylic acid MRF is smaller than the CV of the response to enema, probably because the drug is more closely and completely targeted to the inflammatory region.

Retention enemas of budenoside are used for the treatment of distal ulcerative colitis. Following 4 weeks of treatment with daily enemas containing 2.5 mg of budenoside, the CV of the disease activity index is 135% (Figure 4) [21]. On the other hand, the CVs of the response to maintenance treatments with 3 or 6 mg of oral budenoside MRF for periods up to 12 months are not affected by the dose used or the duration of treatment (Figure 4) [22]. In another study including 258 patients with ulcerative colitis treated with either placebo, 3, 9 or 25 mg of budenoside MRF for 8 weeks, the CVs of the Crohn's disease activity index are 38, 54, 57 and 65%, respectively, suggesting that the doses of budenoside and/or the severity of Crohn's disease increase the CV of the response [23]. As seen with 5-aminosalicylic acid, the response to budesonide enemas is more variable than when using oral budenoside MRF.

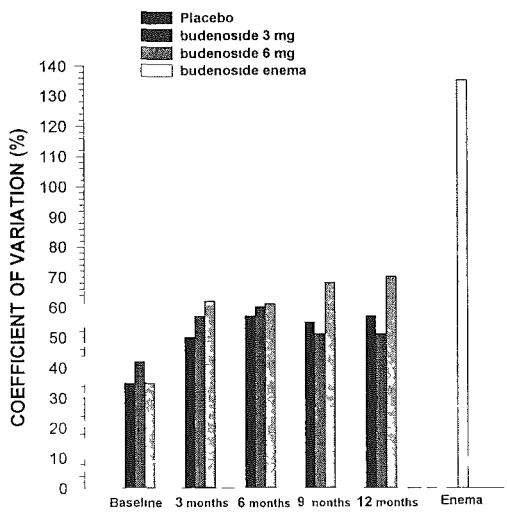

Figure 4. Effect of dose, duration of treatment and route of administration of budenoside MRF on enema on the coefficient of variation of Crohn's disease activity index.

MRF AIMED TO DECREASE THE RATE OF INPUT INTO THE BODY

The drug released from an IRF is rapidly absorbed into the body and as a consequence, the pharmacological response increases abruptly. In the case of drugs affecting cardiovascular homeostasis, the rapid increase in the response triggers reactions that may partially counterbalance the effect, i.e. vasoconstriction and antidiuretic effect with the use of antihypertensive medication and/or diuretics. Whenever the rate of input into the body is slowed by a MRF or an infusion, the efficiency of the drug is enhanced and the response is improved.

The MRF of furosemide increases its diuretic and natriuretic efficiency. The CV of the response to furosemide IRF depends upon the parameter assessed, i.e. the variability of the diuresis is lower than that of the natriuresis, chloruresis or kaliuresis (Figure 5). The CV of the effect of furosemide IRF does not decrease at steady state. On the other hand, after a single dose of furosemide MRF, the CV of the response is higher than that reported with furosemide IRF [24,25]; however, this difference tends to disappear when furosemide MRF is administered to steady state [24]. The CV of the diuretic, natriuretic, and chloruretic efficiency of furosemide MRF also tends to be higher than the CV of the efficiency of furosemide IRF [25].

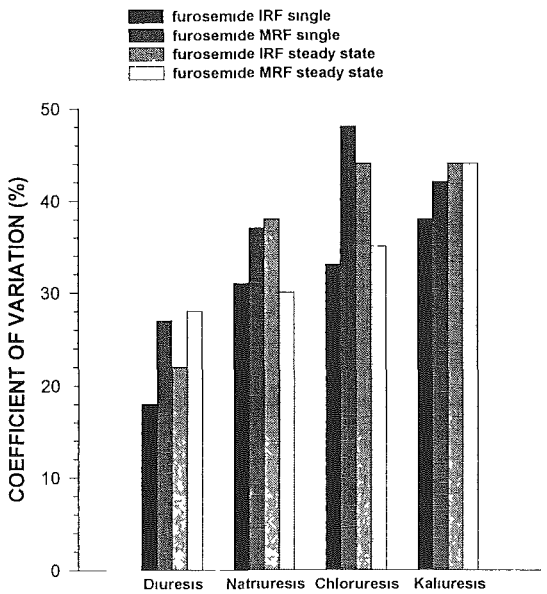

Figure 5. Repercussion of the formulation and the duration of treatment of furosemide on the coefficient of variation of the parameters assessing the response to the diuretic.

The influence of the formulation on the variability of the natriuretic and diuretic responses to diuretics in patients with cardiac, hepatic or renal pathology has not been documented. However, the effect of a continuous infusion of furosemide has been compared with the response to furosemide given as an i.v. bolus q8h to patients with congestive heart failure. Even if the diuretic and natriuretic efficiency of infused furosemide is greater than with the bolus, the CV of the diuresis is not affected by the form of administration [38 v.s. 30%, respectively), but the CV of the natriuresis is greater following the infusion of furosemide (85% v.s. 60%) [26]. Even if the infusion of bumetanide to patients with chronic renal insufficiency is more efficacious than the bolus, the variability of the response is not affected by the mode of administration. The CV of the diuresis (18%) is smaller than the CV of the natriuresis (27%), variability that is more than doubled when the natriuretic efficiency of bumetanide is taken into account, i.e. around 62% [27].

In healthy volunteers, at similar plasma concentrations, the infusion of nifedipine reduces diastolic blood pressure much more efficiently than does a bolus of nifedipine. Compared to the i.v. injection, the CV of the antihypertensive response of nifedipine is not changed by its infusion. On the other hand, the CV of the increase in heart rate is reduced by 33% with the infusion, probably secondary to diminished homeostatic responses as reflected by a smaller increase in heart rate [28]. When nifedipine is given orally as an IRF capsule or a MRF tablet, the CV of the decrease in diastolic blood pressure is greater than that observed using the i.v. route, but the formulation does not affect the variability. The CVs of heart rate and plasma noradrenaline concentration are higher with the MRF than with the IRF [29].

Used as an antihypertensive agent, in patients with moderate essential hypertention at doses ranging from 30 to 60 mg tid for 6 to 8 weeks, nifedipine IRF effectively reduces systolic and diastolic blood pressure with a rather uniform response. The position of the patient does not affect the CV of the effect of nifedipine on systolic blood pressure, i.e. 12.7% supine v.s. 14.5% upright [30,31]. However, the CV of supine systolic blood pressure is higher than the CV of diastolic blood pressure. On the other hand, compared to the supine position, the CV of diastolic pressure and of heart rate almost double in the upright position [31]. By reference to the IRF, nifedipine MRF 20 mg bid or 30 mg od do not modify the CV of systolic pressure, but increase the CVs of diastolic pressure and of heart rate (Figure 6) [32]. Doses of nifedipine up to 90 mg daily do not modify the CV of the response [33].

The CVs of systolic and diastolic pressure under nifedipine GITS (osmotic pump given od) are very similar to those reported with nifedipine CC (coat-core od), independently of the dose [34] or of the study [34,35], i.e. lower than 10%. The variability of the response is closely associated to the choice of the parameter selected to evaluate the response to nifedipine. When the response assessed is the change from baseline values, the CVs for the changes in systolic and diastolic pressures and for heart rate induced by nifedipine GITS are 80, 120 and 610%, respectively [36]. These values contrast with the figures of around 10% when the absolute value of blood pressure or of heart rate is taken into account. Compared to Caucasians with moderate hypertension, specific pathologic conditions like hypertensive crisis [37], and chronic renal insufficiency and long term dialysis [38] do not affect the CV of the response to nifedipine.

In patients with stable angina, the CV of the response to nifedipine IRF changes according to the parameter assessed, i.e. it is 44% for the duration of exercise to depress 1 mm the ST segment, 29% for the time required to present chest pain, and 18% for the total duration of the exercise. Compared with nifedipine IRF, nifedipine MRF bid increases the CVs of the time

required to present chest pain and of exercise duration, although nifedipine MRF od augments only the CV of the total duration of exercise [39,40].

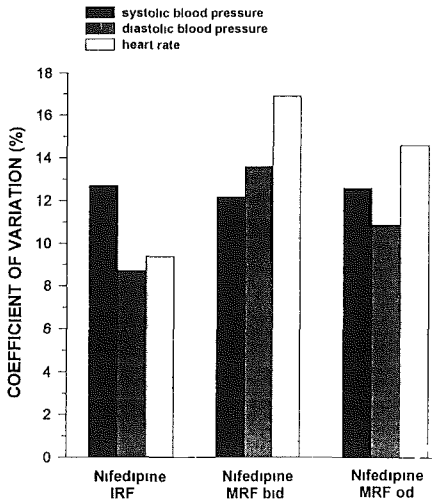

Figure 6. Repercussion of the formulation IRF and twice-daily (bid) or once daily (od) MRF of nifedipine on the coefficient of variation of blood pressure and heart rate.

In patients with mild to moderate hypertension, the repercussion of the formulation on the variability of the pharmacological response to daily doses of 240 or 480 mg of verapamil is minimal, i.e. at similar dosages, the CVs of the systolic and diastolic blood pressures, heart rate and PR interval are always in the range of 8 to 16% [41].

Diltiazem is extensively used as antihypertensive and as an antianginal agent. When diltiazem is given as an IRF at daily doses ranging from 180 to 360 mg to hypertensive patients, the CVs of supine or upright systolic and diastolic blood pressures are around 10% [42]. The use of diltiazem MRF bid does not change the CVs of systolic or diastolic blood pressure [43-46], but a MRF od decreases the CVs of upright systolic and diastolic blood pressure [47,48]. The CVs of heart rate are close to 16% with diltiazem IRF or MRF bid [42-46], and only 10% when MRF od is used [47,48]. The CVs of the effect of diltiazem MRF od on systolic or diastolic blood pressures remains unchanged as the daily dose is increased from 240 to 360 or 420 mg [47].

The CVs of the parameters assessing the effect of diltiazem on the treatment of stable exertional angina are four fold greater (33%) than the CV of the antihypertensive effect of diltiazem (8%). Contrasting with nifedipine, the CVs of the effect of diltiazem on the time to depress 1 mm the ST segment, the time to provoke chest pain and the effect on exercise duration are similar, i.e. around 30%. Compared to diltiazem IRF [49], diltiazem MRF bid [45,49] or MRF od [50,51] do not change the CV of these parameters. The dose of diltiazem

MRF bid (120 or 180 mg) [49] or od (180 or 300 mg), and the brand (Cardizem®, Tildiem® and Diltiazem SR Éthypharm®)[50-52] do not affect the variability of the response, nor does the duration of treatment (6 or 10 weeks) [45].

Compared to the IRF, prazosin MRF augments the antihypertensive response [53]. In patients with mild to moderate hypertension, at an average daily dose of 4 mg, by 12 weeks of treatment, the CVs of the response to prazosin IRF are 10 and 11% for the systolic and diastolic blood pressure, respectively [54]. On the other hand, following daily doses of 5 mg of prazosin MRF od, the CV of the systolic blood pressure is reduced to 4.8%, while the CV of the diastolic blood pressure is 11% [55].

In patients with essential hypertension, younger than 65 years given propranolol IRF bid, the CVs of the systolic and diastolic blood pressure and the heart rate range between 8 and 13%. The variability of the response is not affected by the administration of propranolol MRF od [56,57]. Neither the position of the body at which the blood pressure is measured (supine, sitting, or upright) nor the dose of propranolol affect the CV of the response [56,58]. In individuals subjected to an exercise on a bicycle ergometer to achieve a tachycardia greater than 100 beats/min, the CVs of the diastolic blood pressure and heart rate in response to propranolol MRF are lower than after propranolol IRF [57]. In elderly patients with hypertension, the CV of the response to propranolol IRF is less than half (around 4%) that measured in younger patients with essential hypertension (Figure 7), and propranolol MRF does not change the CV of systolic and diastolic blood pressure or of heart rate [59].

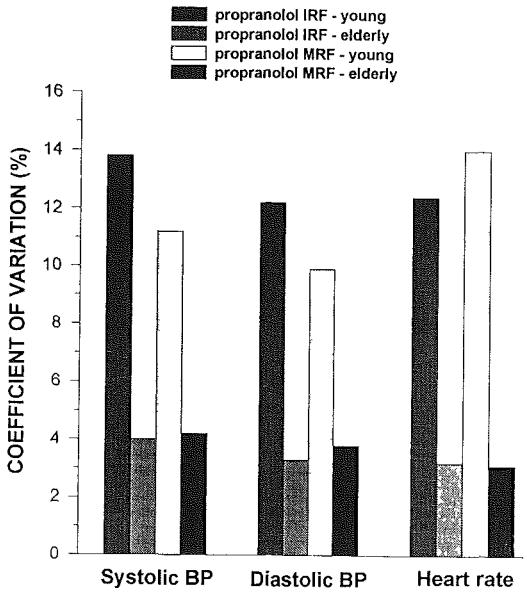

Figure 7. Influence of age of patients with essential hypertension treated with propranolol IRF and MRF on the coefficient of variation of the blood pressure and heart rate.

In patients with stable angina treated with daily doses of 160 mg of propranolol IRF, the CVs of exercise duration and time required to induce chest pain are 24 and 32% respectively. Doses of 80 or 160 mg propranolol MRF od do not affect the CV of exercise duration, but increases the CV of the time to induce chest pain by 55% [60-63], value that is decreased to 29% when the daily dose of propranolol MRF is increased to 320 mg [62].

In patients with essential tremor receiving propranolol IRF 80 mg q8h or propranolol MRF 240 mg od, at trough concentrations the CV of the magnitude of the tremor does not differ between formulations (251 v.s. 224%); at peak plasma concentrations, the CV decreases but it remains higher for the MRF (115 v.s. 168%). Concerning the CV of the tremor level, at trough concentrations it is lower with the MRF (193 v.s. 74%), and does not differ between formulations at peak plasma concentrations of propranolol (99 v.s. 97%). Increasing the daily dose of propranolol MRF to 320 mg does not modify the CV of the magnitude of the tremor or of the tremor level [64].

MRF AIMED TO DECREASE THE INCIDENCE OF UNDESIRED EFFECTS

Since 1980, when Hoftiezer *et al.* [65] reported that aspirin in an enteric-coated formulation prevented almost completely gastroduodenal mucosa damage, many non-steroidal anti-inflammatory drugs (NSAIDs) are marketed in a MRF. The CV of the effect of propionic [66-69] and acetic acid derivatives [70-72] in an IRF on spontaneous pain measured with a VAS ranges between 40 and 80% (Figure 8). The value of the CV depends upon the parameter

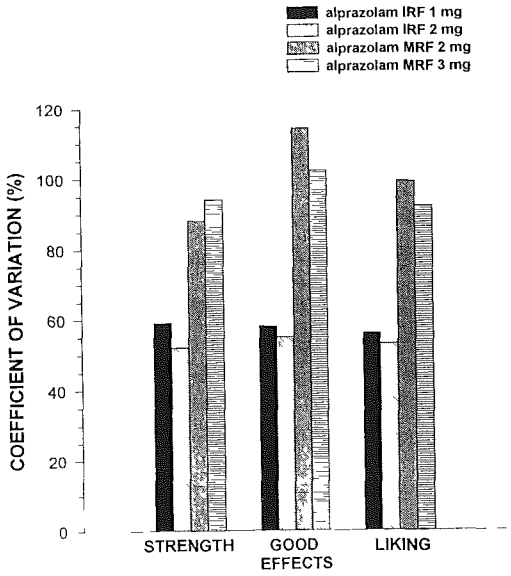

Figure 8. Effect of dose and formulation of alprazolam on the coefficient of variation of the parameters assessing abuse liability of alprazolam.

considered, i.e. 30% for pain on active motion, 17% for quality of sleep, and 14% for spine flexion [65]. The inter-drug variability in CV does not appear associated with the disease treated, i.e. osteoarthritis of several articulations [66,70], osteoarthitis of the knee [72], rheumatoid arthritis [68] or dental impaction pain [69], but rather to the method used to assess the effect of the NSAID on pain and on quality of life of the patient. Naproxen [67] or etodolac [72] response when assessed as the sum of the VAS of individual values of pain standing, walking, night and passive, or as an overall assessment allows CV estimates of 40%. A MRF of propionic acid and acetic acid derivatives does not change the CV of the response. In the case of ketoprofen, by reference to the IRF, the MRF reduces the CV of its effect on spontaneous pain by 50%, without affecting the CV of the measure of pain on active motion, quality of sleep and spine flexion [66].

The CV of the response to sulfonylureas such as glipizide IRF is associated to the parameter measured, to the response itself and to the time of drug utilization. For instance, in "responders" to ≤20 mg of glipizide IRF, at 10 weeks, 1.1 and 2.2 years, the CVs of fasting blood glucose (FBG) are 7, 12 and 23%, and the CVs of HbA_{1c} are 6, 10 and 10% respectively. In "non-responders", at 10 weeks, 1.1 and 2.2 years, the CVs of FBG are 14, 21 and 31% and of HbA_{1c} 14, 15 and 10% respectively [73]. A MRF of glipizide has been released assuming that the incidence of hypoglycemic reactions will be reduced. Following daily doses of 5 to 60 mg of glipizide MRF for 15 weeks, the CVs of FBG and of HbA_{1c} average 31% and 19%, respectively, independently of the dose [74]. Ageing does not influence the CV of the effect on BFG of daily doses of 10 and 20 mg of glipizide MRF, although when FBG is estimated 24 hours (nadir) after drug intake, the CV increases to 41% [75]. Concerning another sulfonylurea, glibenglamide, the formulation did not affect the CVs of its antidiabetic effect, i.e. 15% and 13% for the IRF and MRF, respectively [76].

The variability in the response to the combination of L-dopa and carbidopa IRF (Sinemet®) is influenced by the parkinsonian sign assessed. The CVs of the Hoehn & Yahr stages and the Unified Parkinson's Disease Rating Scale (UPDRS) are 26 and 27%, respectively, while the CV of the Northwestern University Disability Scale (NUDS) is 39% [77]. MRFs of antiparkinsonian drugs are marketed to reduce undesired effects and to improve compliance. The CVs of the rating scales are not modified by the use of Sinemet CR® a MRF [77,78]. L-dopa combined with benserazide IRF (Madopar®) reduces the CVs of the Hoehn & Yahr stages and NUDS to 12 and 18%, respectively, but enhances the CV of the UPDRS to 51% [79]. Compared to Madopar®, the MRF (Madopar HBS®) does not modify the CVs of the rating scales assessed [79].

By comparison to plain diazepam tablets, diazepam MRFs provide anxiolytic effect with less side effects, may not cause an acute feeling of high, and reduce the development of "symptom-drug intake". As depicted in table 1, with diazepam IRF the value of the CV is associated to the test conducted. The time the tests are conducted does not influence the CV, nor does the duration of treatment with diazepam (8 days), except for the CV of the digit symbol substitution test, which decreases on day 8, 3 h after drug administration. At days 1 and 8, the CV of the digit symbol substitution test is lower for diazepam MRF than for IRF at 1.5 h but not at 3 h. At day 1, the CV of the cumulative reaction time is greater with diazepam MRF than with IRF [80]. On day 8, 3 h after drug intake these differences tend to fade. No data is available to assess the influence of the formulation on the variability of the response to diazepam in patients. In patients with anxiety, the CVs of total scores for all symptoms increase from ≈34% to ≈63% and 92% with the duration of treatment with

diazepam MRF, i.e. 0, 1 and 3 weeks, respectively [81].

Table 1.
Coefficient of variation of objective tests performed 1.5 and 3 hrs after the intake of 15 mg of IRF diazepam or of 20 mg of MRF diazepam by 9 healthy volunteers for 8 days

	DAY 1		DAY 8	
	1.5 h	3 h	1.5 h	3 h
Digit symbol substitution/3 min				
Diazepam IRF	15.7	19.7	12.8	10.6
Diazepam MRF	10.2	15.2	8.0	10.3
Tracking error severity				
Diazepam IRF	61	73	58	72
Diazepam MRF	58	65	73	68
Cumulative reaction time (sec.)				
Diazepam IRF	6.7	6.9	9.7	7.6
Diazepam MRF	10.8	14.5	9.4	7.7
Maddox wing (d)				
Diazepam IRF	66	58	64	66
Diazepam MRF	89	83	65	61

In patients with panic attacks, by the end of 6 weeks of treatment with alprazolam IRF the CVs of changes in the scores of the battery of tests assessed range between 6 and 13%. Alprazolam MRF is used for the treatment of panic disorders to avoid inter-dose anxiety as well as undesired sedation. In patients of identical characteristics and receiving the same doses of alprazolam MRF, the CV of the effect of alprazolam is smaller than 13% in one study [82], and ranges between 20 and 150% in another study [83]. Compared to alprazolam IRF, abuse liability is decreased by a MRF, however the MRF almost doubles the CV of the parameters assessing abuse liability, i.e. strength, good effects and liking (Figure 8) [84].

The influence of the formulation on the variability of the response to adinazolam depends upon the test evaluated. In healthy volunteers receiving a single doses of adinazolam, the CV of the mean number correct on word learning is 29% with the IRF and 20% with the MRF when plasma concentrations for both formulations are equal (at 6 h). The MRF does not influence the CV of the mean reaction time (≈20%), the mean number of intrusions on delayed recall (≈50%) and the nurse-rated sedation score (≈50%). However, the MRF increases the CVs of the mean number preserved on word learning (from 85 to 135%) and the mean number correct on delayed recall (from 110 to 160%) [85].

CONCLUSIONS

The repercussions of the formulation upon the variability of the pharmacological response are not uniform, so it is difficult to draw general conclusions. The variability of the response is greatly dependent upon the parameter assessed, the disease itself, the age and state of the patient, and the drug and its dosage. The type of formulation, i.e. MRF bid or od, but not the brand influence the variability of the response. For drugs like theophylline, 5-aminosalicylic acid and budenoside a MRF reduces the variability of the response, suggesting that proper targeting in time and/or place are important to an homogeneous response. On the other hand, the formulation does not modify the variability of the response to opioid analgesics, NSAIDs, L-dopa, and diuretics (at steady state). In addition, for antihypertensive and antianginal drugs, such as verapamil, diltiazem, propranolol, and prazosin a MRF does not affect or decreases the variability of the response; however, nifedipine MRF increases the variability of parameters such as diastolic blood pressure, heart rate, time to elicit chest pain and total time of exercise. The differences between calcium channel blockers are possibly associated to the preferential vasodilatation and lack of effect on heart conduction of nifedipine. The variability of sedative and abuse liability effects of benzodiazepines is in general increased by a MRF, possibly due to the marked reduction in the intensity of these undesired effects in some individuals. Finally, the MRF of drugs such as procainamide and glipizide enhances the variability of the desired response, and possibly multiple factors associated with the patient and the drug influence this effect, i.e. the mechanism of action of the arrhythmia, the dose, weight, diet, etc.

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Discussion: Management of variability through dosage form design

L. Aarons:

Could I make a plea to not use coefficient of variation as a measure of variability, in the sense that it is not a measure of variability. For example, you can have plus or minus one at the value of one, and you can have plus or minus one at the value of 100. At one it has got 100% variability, but at 100 it has got 1% variability. In both cases the variability is actually the same: It is plus or minus one at the bottom, and it is plus or minus one at the top. It actually depends on your reference, therefore it is not a measure of variability. I suspect some of the baselines were different here, so whereas the formulation may have had no effect on coefficient of variation, it presumably did have an effect on response. If you compare values at the same level of response, then the comparison is valid.

P. du Souich:

In theory you are correct. However, when considering the pharmacological response to two different formulations, the differences in the desired response cannot be important, otherwise the two formulations could not be considered as bioequivalents. Therefore, the mean values of the effect measured are usually rather close, what may vary is the variability around this mean. I believe that under such conditions the use of the coefficient of variability is not inadequate.

J. Urquhart:

There is another aspect to the nifedipine story that does not quite fit the formalism you have used. The reflex tachycardia approximately occurs in about 40% of patients who take nifedipine in a conventional dosage form. Back in the mid-80s several colleagues and I looked at the pharmacodynamics of this effect. It was evident from what we did that the trigger for reflex tachycardia is a high rate of increase of nifedipine concentrations. We suggested to give nifedipine in a constant rate released in oral dosage form as measure to avoid that major side-effect. That in fact was realised with an oral form of nifedipine in the clinical studies, and it opened up the use of nifedipine as an anti-hypertensive in the American market. It became the biggest-selling cardiovascular drug in history for five or six years until amlodipine came along and exceeded it. This is the biggest story in the whole drug delivery system arena, because the essential incidence of reflex tachycardia with that new dosage form, based on the published clinical data, is essentially zero. It is a real triumph, but a one-off thing because of the peculiarity of that drug and its funny pharmacodynamics.

P. du Souich:

It is important to differentiate desired from undesired response. Drugs to be marketed in a new formulation must be bioequivalent, i.e. it is always presumed that the response elicited by a certain dose is not affected by a formulation. However, when the formulation is changed to reduce a side effect, obviously the mean value of the measured side effect should be decreased. In the case of nifedipine, for the same dose, the desired effect, that is the antihypertensive effect obtained with the modified release formulation is similar to that elicited with the conventional formulation. Although the undesired effect, tachycardia, is reduced.

U. Klotz:

Concerning the example of budesonide and 5-aminosalicylic acid, both drugs are supposed to work topically, and depending on the site of the inflammation you take either the enemas or the modified-release oral preparation. The physician does not care about variation. Enemas are most effective in left-sided colitis, and modified-release preparations are more recommended for the small or upper large bowel. Thus, it always depends on the indication which one you take, because of the topical action.

P. du Souich:

However, in the same studies they did compare the enema and the modified-release formulation. Obviously, there is a bias because they gave both treatments to all the patients, and I agree with you that some of them probably were poorly treated.

N.L. Benowitz:

I am not sure that I understood some of the responses described for the coefficient of variation data from the calcium channel blocker studies. It was my impression that if you look at circadian variation, there is much more circadian variation with immediate release than sustained release calcium blockers. That is one of the theories at least for greater risk of adverse effects of immediate release calcium blockers in hypertensive patients, in terms of coronary events, sudden death, etc. Did you look at circadian variation in your analysis through the coefficients of variation?

P. du Souich:

No, what I am showing is in a group of patients with hypertension who have been treated with both drugs, is the variability of the hypotensive response.

N. Benowitz:

For hypertension the 24-hour response is really a key issue for variability. Were you looking at that, or were you looking at within-subject variations throughout the day?

P. du Souich:

No. They did not study the hypotensive response along the 24 hours, since here antihypertensive agents were usually given 2 or 3 times daily. So I do not include the possible influence of day-time or night-time variability. But the variability was anyway rather low. If again we accept this coefficient of variation as a measure of this variability, it was around 10% compared to 40% in angina, for instance, or much higher for other indications.