

To the Editor

Currently, beta blockers (e.g. metoprolol, atenolol, bisoprolol, esmolol, nebivolol, propranolol, pindolol) are broadly used to treat diseases like hypertension, tachycardia, cardiac arrhythmia, congestive heart failure, essential tremor, migraine prophylaxis, and myocardial infarction for example. Both beta blockers and iodinated radio-contrast media (ICM) are frequently used, so that a relevant proportion of patients undergoing ICM-enhanced computed tomography (CT) or other X-ray related imaging procedures can be estimated to be under treatment with beta blockers. Usually, ICM are well tolerated and safe. However, adverse events (AEs) and hypersensitivity reactions (HSRs) do still occur in a small percentage of patients. Especially, patients at risk will acquire AEs/HSRs. Therefore, the identification of risks is mandatory to efficiently avoid ICM-side effects. While a history of a previous ICM-reaction/-allergy is a well-known risk and a clear indication for a prophylactic task, other risks such as intake of beta-blockers are less clear and therefore, still a matter of debate. Since GPs should be involved in the decision process to safely manage the application of ICM, we summarized the current knowledge concerning beta-blocker medication while undergoing ICM-enhanced radiological imaging procedure.

Do beta blockers increase the risk for CM adverse events?

In the clinical routine, patients are rarely asked if they are taking beta blockers prior to administration of contrast media; however, several reports hold on that beta blockers are risk factors for CM AEs. Currently, the question whether a patient is actually taking beta blockers is included in the ESUR-questionnaire

(http://www.esur.org/guidelines/esur2012_questionnaire_part1.pdf). Unfortunately, further explanations and recommendations are missing. Therefore, it is not clear what should a physician, general practitioner, cardiologist or an internal specialist do. Moreover, in both single cases and observational clinical studies, severe hypersensitivity reactions have reported in patients taking beta blockers who underwent ICM-enhanced radiological procedures [1-4].

The following example is of special interest, because this seems to be a key paper of the beta blocker problematic in association with ICM. Thirty years ago two patients on beta blockers were reported to experience severe adverse events after urography with sodium meglumine diatrizoate (an ionic CM of high osmolality) [2]. The author of these reports theorized that beta blockers stimulate the release of histamine by mast cells or leukocytes or potentiate histamine's action. Moreover, he recommended that radiologists performing excretory urography on patients taking beta blockers should take the following precautions:

- Recommend the withdrawal of the beta blockers for 2 to 3 days before the examination when possible
- Administer an oral antihistamine 2 hours before the injection.

Six years later Lang et al. found that the risk of bronchospasm was associated with beta-blocker exposure (OR, 3.73; 95% CI, 1.18 to 11.75; $P = .025$) and with asthma (OR, 16.39; 95% CI, 4.30 to 62.46; $P = .0001$) [1]. The risk of major and life-threatening reactions was associated with the presence of a cardiovascular disorder (OR, 7.71; 95% CI, 1.04 to 57.23; $P = .046$) [1]. Among patients with severe reactions, the risk of hospitalization was elevated by the presence of cardiovascular disorder ($P = .001$), exposure to beta blockers (OR, 7.67; 95% CI, 1.79 to 32.85; $P = .029$), or asthma (OR, 20.7; 95% CI, 1.21 to 355.55; $P = .065$) [1]. Cardiovascular diseases (CVD) *per se* increase the risk of severe or fatal anaphylaxis, and some medications for CVD including beta-adrenergic blockers and ACE inhibitors potentially exacerbate anaphylaxis or make it more difficult to treat [4]. Another study showed that antihypertensive medication use (i.e. beta-blockers, ACE inhibitors) is associated with increased organ system involvement and increased odds of hospital admission, independent of age, gender, suspected trigger, or preexisting lung disease [3].

Other researchers found that the treatment of anaphylaxis was different under beta blockers; the inhibiting effect of epinephrine on the immunological activation of human basophils was reversed by the beta blocker propranolol [5].

Beneficial effects of beta blockers

On the other hand more recent papers dealing with this topic did not confirm negative influences from the intake of beta blockers [6-9]. For example, it could be shown that both isoprenaline and salbutamol act as β_2 -adrenoceptors to suppress IgE-mediated mediator release from cultured human mast cells [6].

Moreover, beta-blockers are regularly given to optimize the heart rate in primary percutaneous coronary interventions. Recent investigations show that the use of intravenous β -adrenergic blockade before coronary CT angiography is a safe prophylactic tool to optimize the heart rate [7, 8]. Aggarwal et al have presented similar results concluding that beta-blocker premedication does not increase the frequency of allergic reactions from coronary CT angiography [9].

Do gadolinium-based contrast agents (GBCA) increase the risk for AEs?

To date, beta blockers have been observed to be risk factors for iodinated CM-induced hypersensitivity reactions only [1-4], while GBCA have not been mentioned in this context. GBCA are generally associated with far fewer hypersensitivity reactions than ICM: the overall rate of adverse events with GBCAs is 0.1% [10]. Consequently, severe manifestations such as anaphylactic shock are also less frequently observed after the administration of GBCA. The reduced overall frequency of reactivity might be the reason why beta blockers have not attracted attention as risk for AEs as well. This fact may implicate a possible association with a beta blocker intake in future, because of the still increasing trend of the use of GBCA.

Conclusion and practical recommendation

Evidence in the medical literature suggests that beta blockers do not increase the frequency of anaphylaxis, but do increase the risk for severe anaphylaxis and for treatment-refractory conditions [3, 4, 11]. Interestingly, the older the paper the more harmful the CM-application in

concert with patients who receive beta blockers. This fact possibly might reflect the use of less tolerated ionic CM of high osmolality in former times, and currently the more better tolerated non-ionic CM of low-/iso-osmolality.

Therefore, beta blocker receiving patients who will undergo ICM-enhanced radiological examinations should be asked as to whether they tolerate the ICM-application. If the answer is yes, no further prophylactic actions are necessary. If the answer is no, in cases of elective examinations a diagnosis is recommended to find out individual tolerable ICM-compounds; in emergency cases radiologists should be informed to be prepared (e.g. by an anesthesia-stand-by) (see also figure 1).

References

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