Patients with elevated international normalized ratio due to oral anticoagulants: An evaluation of risk factors

Sir,

Excessive anticoagulation is a frequent complication of anticoagulant therapy, associated with high morbidity and mortality rates. It has been estimated that the risk of bleeding almost doubles for each one-point increase in the international normalized ratio (INR) above 3.0.

We aimed to determine the epidemiological and clinical characteristics, as well as, the factors associated with the outcome of patients admitted with prolonged INR due to anticoagulants. We examined the medical records of all patients on oral anticoagulant therapy, who were admitted to our ward with prolonged INR (>4), between the years 2010 and 2012. We recorded numerous parameters of interest, such as comorbidities, co-medications, and complications observed during their hospitalization. Descriptive statistics were used to express patients’ epidemiological data while logistic regression analysis was performed to associate clinical characteristics with a bad outcome, defined as patient’s death. The study protocol was approved by the Ethics Committee of the General Hospital of Larissa.

Sixty-six patients (39 male) were enrolled in the study, with a mean age (± standard deviation) 78 years (±9.08) and mean INR value on admission 9.57 (±4.77). The vast majority of patients (95%) was on therapy with acenocoumarol, while the mean time of hospitalization in days was 4.59 (±4.53). Among these, 86.3% were receiving anticoagulants for atrial fibrillation; 31.8% had recently started anticoagulant medication (<30 days). 28.7% presented complications, with acute renal failure being the most common (12%). Ecchymosis was the most common among bleeding complications (30.3%), followed by lower gastrointestinal bleeding (16.6%). 31.8% were in need of blood transfusion, while 84% required Fresh Frozen Plasma transfusion. Salient characteristics of the patients included in the study are summarized in Table 1.

Totally, 10 deaths (15%) occurred in our cohort. The regression analysis demonstrated a statistically significant association between the poor outcome and the following parameters: Occurrence of any type of complications, more than 5 days of hospitalization, hypovolemic shock on admission, concomitant use of cephalosporins, history of stroke, and history of pulmonary embolism [Table 2].

All antibiotics have the potential to increase the degree of anticoagulation in patients undergoing warfarin therapy. However, most cephalosporins do not normally interact with the oral anticoagulants. Moreover, severe bleeding events in patients concurrently receiving cephalosporins and warfarin, have mainly been described in isolated case reports. To our best knowledge, this is the first study to demonstrate a significant association between the use of cephalosporins and the risk of death, in subjects with elevated INR.

To conclude, patients with prolonged INR receiving anticoagulation, represent a high-risk group of hospitalized subjects, especially when comorbidities are present. Our study proposes certain factors, which could potentially work as predictors of bad outcome in patients with elevated INR due to oral anticoagulants. Further studies are required, in order to draw conclusions about the role of these factors and to recommend measures to minimize the risks due to anticoagulant therapy.

Table 1:
Epidemiological and clinical characteristics of the patients included in the study

| Parameter                                      | Value (%) |
|-----------------------------------------------|-----------|
| Male/female (n)                               | 39/27     |
| Age                                           | 78±9.08*  |
| INR on admission                              | 9.57±4.77*|
| Days of hospitalization                        | 4.59±4.53*|
| Atrial fibrillation                            | 86.3      |
| Recent start of anticoagulant medication (<30 days) | 31.8      |
| Presence of complications                      | 28.7      |
| Blood transfusion                              | 31.8      |
| Transfusion of fresh frozen plasma             | 84        |

*Mean±SD. INR=International normalized ratio, SD=Standard deviation

Table 2:
Factors significantly associated with bad outcome in patients receiving anticoagulant drugs

| Parameter                              | P       |
|----------------------------------------|---------|
| Occurrence of complications            | <0.01   |
| >5 days of hospitalization             | <0.01   |
| Hypovolemic shock on admission         | 0.03    |
| Concomitant use of cephalosporins      | 0.04    |
| History of stroke                      | 0.03    |
| History of pulmonary embolism          | 0.04    |

P<0.05 considered statistically significant
Sir,

I read with great enthusiasm the article by Sahoo et al. [1] entitled “Chemo-preventive potential of Apium leptophyllum against DMBA induced skin carcinogenesis model by modulatory influence on.” In the study, flavonoids of Marsh Parsley showed a strong protective effect against induced carcinogenesis. Due to the advances of molecular sciences, in isolation and structure elucidation techniques of various natural products, it will be interesting to determine specific bioactive compounds obtained from the flavonoid fraction of this plant. However, it is not clear, what is the real molecular basis for the observed protective effect, and which bioactive compounds produced this effect. Currently, several different molecular targets of flavonoids are discussed [2]. Medicinal chemists and pharmacologists have studied mainly the anti-oxidative properties of flavonoids, and their metabolites, but flavonoids may exert effects in cells through the influence of anti-apoptotic and pro-proliferative signaling pathways. During DMBA-induced carcinogenesis, protective effect can also be caused by suppression of kinase signaling cascades such as mitogen-activated protein kinases/extracellular signal–regulated kinase, phosphoinositide 3-kinase/Akt, or inhibit induced activation of epidermal growth factor receptor-related pathway [Figure 1] [2-4]. It can be a critical step in this carcinogenicity. However, these proliferative cascades are activated by DMBA irritation, and thus prevention of their activation by flavonoids might play an additive role in suppression of induced carcinogenesis [5,6].

Blocking of these pathways leads to a reduction of expression of some proliferative and anti-apoptotic factors and has been shown that these signaling pathways have a key role in the early phases of carcinogenesis [6]. Consequently, compounds from the flavonoid fraction of A. leptophyllum should be isolated, structurally characterized, and screened for their bioactivity in cell cultures and murine models. Whether, a part of the chemo-protective effect is not caused by the suppression of kinases related signaling pathway responsible for the cell growth and survival should be evaluated.

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