Update on caffeine consumption, disposition and action

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Abstract

This report represents a current summary of the caffeine contents of various commercial products, and provides data on the spectrum of caffeine intake levels in man. A summary of the substance’s pharmacokinetics describes information on its disposition in the body. The effects of caffeine are related to its interaction with adenosine receptors.

1. Introduction

To evaluate any possible toxic effects associated with caffeine, described in the following reports, it is desirable to have an indication as to the normal levels of exposure to caffeine from various sources. Coffee undoubtedly serves as the primary source of caffeine in the adult, but caffeine is also contained in tea and cocoa, many soft drinks and several drug preparations, including many over-the-counter products. Caffeine intake varies widely, since half the population does not drink coffee, and some individuals consume very substantial amounts. Therefore, knowledge of the range of caffeine consumption is helpful in evaluating the relevance of experimental studies intending to duplicate the human situation.

After its oral ingestion, caffeine is absorbed, is distributed to various tissues, and broken down to metabolites with variable pharmacological actions, which are then excreted. Pharmacokinetics describes these various processes as a function of time after caffeine intake, and may provide an explanation as to the duration and magnitude of biological effects observed. Caffeine is believed to interact with receptors for which adenosine is the normal substrate.

Investigators frequently have reported their observations on caffeine following the ingestion of coffee, under the assumption that any effect observed must be due to caffeine. However, there are several hundreds of other components in coffee, and it is vital to ascertain that these effects are indeed due to caffeine. Although caffeine probably is the most physiologically active ingredient of coffee, these other components can provide additional pharmacological effects. Obviously, this complication can be overcome by the administration of pure caffeine; however, this approach may be impractical. As decaffeinated coffee is extremely low in caffeine, a comparison with regular coffee could further substantiate that any observed effect is related to caffeine. However, the removal of caffeine from coffee may also lead to the extraction of other components with biological activity. The supplementation of decaffeinated coffee with an exact amount of caffeine is a more precise way of measuring the effects of caffeine (Denaro et al., 1990).

2. Caffeine content of caffeine in its most common sources

The preparations of coffee commonly used are anything but uniform. Coffees grown in different parts of the world differ genetically in their composition, so that the amount of caffeine per gram of bean will not be identical. There are numerous preparations of coffee, such as percolation, filtration, boiling, instant, espresso, etc., each of which will extract different amounts of caffeine per gram of coffee bean. The quantity of coffee beans employed, the degree of roasting, the fineness of grinding and the amount of water used for extraction, as well as the length of time of extraction, will differ according to the preparer. The habits of coffee consumption differ in geographic areas of the world, as does the amount of coffee drunk. As a result, the content of caffeine in a cup of coffee varies considerably.
There also are great inter-individual factors which modify the disposition of caffeine after its consumption, so that the levels of caffeine achieved in plasma would provide a more accurate reference for comparison. Most importantly, the analytical procedures used to assay caffeine have been refined extensively in the past few decades. Whereas formerly ultraviolet absorption of extracts provided acceptable data on caffeine content of various preparations, the use of HPLC and GC has further refined the quality of the analytical procedures to measure caffeine more accurately and specifically. Many of the analyses reported before 1975 may therefore be less precise.

Estimates of the content of caffeine in coffee, tea, chocolate candy, soft drinks and commercial drug preparations are listed in Table 1, derived from some of the most reliable reports among the many analyses in the literature (Gilbert et al., 1976; Lelo et al., 1986; Stavric et al., 1988). Despite the great variation in caffeine content in an individual cup of coffee, there is general agreement as to mean values. This important topic has been reviewed in detail by Barone and Roberts (1996).

In the United States, a typical coffee drinker consumes a mean of 2–4 cups of coffee/day, leading to the daily ingestion of about 4 mg caffeine/kg of body weight. Heavy coffee drinkers, at the 90th percentile, may take in about 5–7 mg/kg, and in some individuals consumption may reach 15 mg/kg. However, since only about half of the total population of 10 years or older drink coffee, the daily consumption of caffeine on a per capita basis from all sources has been estimated to be only about 2.4 mg/kg (Chou, 1992). For children between the ages of 5–18 years, the total intake of caffeine from all sources probably averages about 1 mg/kg.

The content of caffeine in tea is lower than that in coffee, and depends on the source and packaging of the tea and the extent of time allowed for extraction (a maximum is reached after about 5 min of brewing). The amount of caffeine in different soft drinks is more consistent, but for drug preparations it has varied over the years. “Energy drinks” represent a new category of beverages that exceed the US regulated concentration of caffeine in soft drinks (200 ppm, or approximately 6 mg/ounce). For example, Red Bull, contains 80 mg caffeine

Table 1
The content of caffeine, expressed as a mean, in a cup of coffee has been calculated to represent the unit as consumed. This eliminates the variations produced by different cup volumes, which may be between 40 and 300 ml. Chocolate is calculated per ounce (28 g), soft drinks 12-oz cans except for Red Bull, and drug preparations are per tablet or capsule

<table>
<thead>
<tr>
<th>Product</th>
<th>Reference</th>
<th>Coffee, mg per serving</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Coffee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percolated</td>
<td>82</td>
<td>80</td>
</tr>
<tr>
<td>Drip</td>
<td>84</td>
<td>112</td>
</tr>
<tr>
<td>Instant</td>
<td>71</td>
<td>60</td>
</tr>
<tr>
<td>Decaffeinated</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Espresso&lt;sup&gt;a&lt;/sup&gt;</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Tea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bag</td>
<td>40</td>
<td>27</td>
</tr>
<tr>
<td>Leaf</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Instant</td>
<td></td>
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<tr>
<td>Cocoa</td>
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<tr>
<td>Milk chocolate</td>
<td></td>
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<tr>
<td>Baking chocolate</td>
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<tr>
<td>Soft drinks</td>
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<tr>
<td>Coca Cola, Diet Coke</td>
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<tr>
<td>Dr. Pepper</td>
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<tr>
<td>Pepsi Cola</td>
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<tr>
<td>Dr. Pepper Diet Sun Drop&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Royal Crown Edge&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Energy drinks (e.g. Red Bull, 250 ml, 8.8 oz can)</td>
<td></td>
<td></td>
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<tr>
<td>Drug preparations</td>
<td></td>
<td></td>
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<tr>
<td>Excedrin, extra strength</td>
<td></td>
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<tr>
<td>Darvon Compound-65</td>
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<tr>
<td>Caffedrin</td>
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<tr>
<td>Vanquish</td>
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</tbody>
</table>

References: A. Stavric et al. (1988); B. Lelo et al. (1986); C. Gilbert et al. (1976); D. Barone and Roberts (1996); E. Chou (1992).

<sup>a</sup> Very limited data. Large variations in caffeine content have been reported, from 40 mg (International Food Information Council, http://www.ificinfo.health.org) to 116 mg caffeine per cup (D'Amicis and Viani, 1993).

<sup>b</sup> Data from National Soft Drink Association: http://www.nsda.org.
in a 250 ml can, which is in the concentration range of a
serving of coffee.

2.1. Physiological disposition of caffeine

Data on the pharmacokinetics of caffeine provide
information as to how much of ingested caffeine reaches
its target receptors, the duration of active concentra-
tions at the receptor sites, and the effects of repeated
intake in relation to the observed intensity of action
over time.

When ingested orally, caffeine is rapidly absorbed,
distributes throughout total body water (including the
fetus), and reaches a peak plasma level between 30 and
75 min. Animal studies have demonstrated that the caf-
fene concentration in mouse brain is about 80% that of
plasma (Kaplan et al., 1989), and that value probably
also holds for man.

Plasma levels of caffeine after the consumption of up
to about 6 cups of coffee per day generally ranged
between 2 and 6 mg/l (Lelo et al., 1986). In another
study, plasma caffeine levels peaked at about 3 mg/l
after 4.2 mg/kg/day of caffeine added to decaffeinated
coffee, and reached 13 mg/l after 12 mg/kg/day of caf-
feine, following the ingestion of 6 cups during a 12-h
interval (Denaro et al., 1990). Following the ingestion
of a capsule containing 2 mg/kg of caffeine (corresponding
roughly to 2 cups of coffee for an adult), the plasma
level reached a value of about 3 mg/l, and plateaued at
7.5 mg/l after a 4 mg/kg dose of caffeine (Benowitz et
al., 1995). This mode of administration is convenient
and precise, but does not mirror precisely the absorp-
tion of caffeine after drinking sufficient cups of coffee to
contain the same quantity of caffeine.

In the human, slightly more than 80% of adminis-
tered caffeine (1,3,7-trimethylxanthine, mol. wt 194) is
metabolized by demethylation to paraxanthine (1,7-
dimethylxanthine) via liver cytochrome P-450 1A2, and
about 16% is converted to theobromine and theo-
phylline, (3,7- and 1,3-dimethylxanthine, respectively)
(Benowitz et al., 1995). With repeated caffeine con-
sumption during the day, as represented by the typical
coffee drinker, paraxanthine levels in the plasma reach
about 2/3 of those of caffeine at steady state (Denaro et
al., 1990). These metabolites are then further broken
down in the liver by additional demethylations and oxi-
dation to urates, and an acetylated uracil derivative is
also formed. About a dozen metabolites are recovered
in the urine, but little (less than 3%) or none of the
ingested caffeine is found in urine (Kalow and Tang,
1993). The disposition of caffeine in animals frequently
differs from that in man.

Clearance values for caffeine are approximately 1–3
mg/kg/min in both men and women (Kaplan et al.,
1997) after low-dose caffeine intake. With higher caf-
feine doses, clearance is diminished, largely because of
saturable metabolism of paraxanthine and its decreased
clearance. Thus, paraxanthine accumulates in plasma,
which leads to a reduction in caffeine clearance. This
dose-dependency in caffeine after chronic dosing pro-
duces disproportionate increases in plasma levels, and
since paraxanthine shares many of the pharmacological
actions of caffeine, undoubtedly contributes to any bio-
logical effect after high levels of consumption of caffeine
(Denaro et al., 1990). The half-life of caffeine has been
reported as 4–5 h with modest intake of coffee, but
increases after higher levels of intake (Kaplan et al.,
1997), or with impaired liver function. The half-life is
extended significantly in early infancy and during the
later stages of pregnancy, and is reduced for cigarette
smokers (reviewed in Busto et al., 1989, Chou, 1992;
Chou and Benowitz, 1994).

2.2. Likely mechanism of pharmacological action

Earlier it was believed that the action of caffeine was
related to the inhibition of phosphodiesterase, leading
to increased concentrations of cyclic AMP. However,
this inhibition requires caffeine dosages much higher
than those consumed through beverages or foods. A
more likely mechanism, following the intake of low
doses of caffeine, involves antagonism of adenosine
receptors which are present in brain, blood vessels, kid-
neys, heart, the GI tract and the respiratory tree
(reviewed in Chou and Benowitz, 1994). Daly and Fred-
holm (1998) concluded that the stimulatory effects of
caffeine were largely due to blockade of A2A receptors
that stimulate GABAergic neurons of inhibitory path-
ways to the dopaminergic reward system of the striatum.
However, blockade of A1 receptors was considered to
also play a role. High affinity A1 receptors inhibit ade-
nylate cyclase, whereas low affinity A2 receptors stimu-
late the activity of that enzyme (Daly, 1993). The
functions of adenosine receptors and the role of caffeine
have been recently reviewed (Svenningsson et al., 1999).

Tolerance to the actions of caffeine has been noted
after its regular consumption, and this tolerance dis-
sipates after its discontinuation. Resensitization to caf-
feine appears to be complete by 3 days (reviewed in
Benowitz et al., 1995). In the rat, tolerance to caffeine
has been associated with an increase in adenosine
receptor activity and a shift of A1 receptors to the high
affinity state, leading to an increased functional sensi-
tivity to adenosine and a decrease of β-adrenergic
activity (reviewed in Chou, 1992; Daly, 1993).

The behavioral stimulant potencies of caffeine and
several metabolites, such as paraxanthine and theo-
phylline, correlate with their affinity for occupation of
adenosine receptors. (Kaplan et al., 1997). These effects
include mental stimulation, systemic catecholamine
release, and sympathetic neural stimulation, leading to
an increase in blood pressure and lipolysis with an
increase in plasma free fatty acid concentrations (reviewed in Benowitz et al., 1995; Kaplan et al., 1997). Paraxanthine contributes to the pharmacological action of caffeine (Benowitz et al., 1995), especially during long-term caffeine consumption at higher doses when there is accumulation of paraxanthine in plasma (Denaro et al., 1990). The plasma levels of theophylline produced from caffeine are probably too low to exert any additional actions.

References