Introduction

Techniques and applications for contrast-enhanced magnetic resonance angiography (CE-MRA) have developed rapidly in recent years, due largely to advances in hard- and software design. The advent of innovative new contrast agents with properties distinct from those of the traditional, extracellular gadolinium agents promises to further expand the clinical applicability of CE-MRA, making this the modality of choice for diagnostic imaging of the vasculature. With few exceptions, most of the commercially available contrast agents are not approved directly for CE-MRA \[1,2\]. The present review summarizes the properties and imaging applications of currently available contrast agents which are in routine use in CE-MRA. Described also are those agents in clinical development which may one day find utility in CE-MRA.

Classification of Contrast Agents for CE-MRA

Contrast agents for CE-MRA fall into two broad categories, those based on gadolinium which are predominantly paramagnetic in nature, and those based upon iron oxide particles which are superparamagnetic in nature. Agents in the former category can be sub-classified further into agents with no capacity for interaction with intravascular proteins and those with either weak or strong capacity for protein interaction. Similarly, agents in the latter category can be sub-divided on the basis of the size and coating of the iron oxide particles present. A summary of contrast agents that are either available or in advanced stages of development is given Fig. 1. A brief outline of these agents has been given elsewhere [3].

Paramagnetic Contrast Agents: First Pass Gadolinium Agents

Currently, seven gadolinium contrast agents are approved in one or more countries of the world and an eighth is in the final stages of the approval process (Fig. 2). Although all are suitable for use in first-pass CE-MRA, few agents are actually approved specifically for this indication. Six of these seven agents possess no capacity for interaction with serum proteins and can be considered “conventional” first generation gadolinium chelates (Fig. 1, column 1; Fig. 2a-f). The seventh agent, gadobenate dimeglumine (Fig. 2g), possesses elevated T1-relaxivity in blood due to a unique capacity among currently available agents for weak, transient interaction with serum albumin. This agent is the first representative of a new class of second generation gadolinium agents (Fig. 1, column 2).

Gadolinium Contrast Agents with no Capacity for Protein Interaction

The group of “conventional” gadolinium agents includes the first compounds to be developed for MRI some 12–15 years ago (i.e. gadopentetate dimeglumine, gadoterate meglumine, gadoteridol and gadodiamide) plus two newer agents (gadoversetamide and gadobutrol). Among these agents five are available as 0.5 Molar formulations and one, gadobutrol, as a 1.0 Molar formulation. Although differences exist between these agents in terms of molecular structure and chemical and physical properties (Table 1) [4], all are non-specific and extracellular in nature and all are excreted unchanged through the kidneys by glomerular filtration. Furthermore, the T1 relaxation rates of these agents are comparable, falling in the range between 4.3 and 5.6 L/mmol • s\(^{-1}\) [4-7]. The similar concentrations and relaxation properties of these
agents generally translate into similar vascular imaging performance when injected at equivalent dose, and, until recently, the choice of which to use was dictated largely by non-radiological factors.

That certain of the “conventional” gadolinium agents might be considered preferable over others for CE-MRA has emerged from the observations of Prince et al. [8] and others [9, 10] who confirmed earlier work [11, 12] in noting that gadodiamide and gadoversetamide interfere with the colorimetric test for serum calcium, resulting in spurious hypocalcemia in routine clinical laboratory investigations. This was shown to be due to the relatively low stability of these agents compared to the other available gadolinium agents (Table 1) and, pertinently, was shown to be a greater problem with higher doses and in patients with renal insufficiency [13]. Notably, high doses of conventional gadolinium agents of up to 0.3 mmol/kg have been routinely used in numerous CE-MRA protocols, particularly those involving large vascular territories such as the run-off vessels [9], and those involving MR angiography of the renal arteries – a frequent procedure among patients with renal insufficiency [14-16].

Another recent observation related to gadolinium chelate stability which may influence the choice of contrast agent for MRI procedures in general concerns the issue of gadolinium retention within the body following possible transmetalla-